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? b 155, 5

       04oct01 14:13:40 User242957 Session D333.2
            $0.00    0.065 DialUnits File410
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     $0.00  Estimated cost this search
     $0.00  Estimated total session cost   0.273 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2001/Oct W4
  File   5:Biosis Previews(R)  1969-2001/Sep W5
         (c) 2001 BIOSIS

      Set  Items  Description
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? s adipocyt? and fatty and acid and binding and protein?

          22287  ADIPOCYT?
         241201  FATTY
        2047524  ACID
        1054757  BINDING
        2653575  PROTEIN?
      S1     630  ADIPOCYT? AND FATTY AND ACID AND BINDING AND PROTEIN?
? s afabp or ap2

             20  AFABP
           1530  AP2
      S2    1547  AFABP OR AP2
? s s1 or s2

            630  S1
           1547  S2
      S3    2049  S1 OR S2
? s s3 and (inhibit? or treat?)

           2049  S3
        1892863  INHIBIT?
        3025980  TREAT?
      S4     590  S3 AND (INHIBIT? OR TREAT?)
? s s4 and atherosclerosis

            590  S4
          69037  ATHEROSCLEROSIS
      S5       0  S4 AND ATHEROSCLEROSIS
? s s1 and atherosclero?

            630  S1
          88239  ATHEROSCLERO?
      S6       8  S1 AND ATHEROSCLERO?
? re

>>>Unrecognizable Command
? rd

...completed examining records
      S7       5  RD (unique items)
? t s7/3,ab/all
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7/3,AB/1 (Item 1 fr[redacted] file: 155)
DIALOG(R)File 155:MEDLIN[redacted])

11598710 21373907 PMID: 11481226
Absence of **adipocyte fatty acid binding protein** prevents the development of accelerated **atherosclerosis** in hypercholesterolemic mice.
Perrella MA; Pellacani A; Layne MD; Patel A; Zhao D; Schreiber BM; Storch J; Feinberg MW; Hsieh CM; Haber E; Lee ME
Program of Developmental Cardiovascular Biology, Cardiovascular Division, and. Pulmonary and Critical Care Division, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA. mperrella@rics.bwh.harvard.edu
FASEB journal (United States) Aug 2001, 15 (10) p1774-6, ISSN 0892-6638 Journal Code: FAS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

7/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11443532 21279103 PMID: 11385507
Lack of macrophage **fatty-acid-binding protein** aP2 protects mice deficient in apolipoprotein E against **atherosclerosis**.
Makowski L; Boord JB; Maeda K; Babaev VR; Uysal KT; Morgan MA; Parker RA; Suttles J; Fazio S; Hotamisligil GS; Linton MF
Division of Biological Sciences and Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA.
Nature medicine (United States) Jun 2001, 7 (6) p699-705, ISSN 1078-8956 Journal Code: CG5
Contract/Grant No.: HL65405-01, HL, NHLBI; T32 DK7061, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The **adipocyte fatty-acid-binding protein**, aP2, has an important role in regulating systemic insulin resistance and lipid metabolism. Here we demonstrate that aP2 is also expressed in macrophages, has a significant role in their biological responses and contributes to the development of **atherosclerosis**. Apolipoprotein E (ApoE)-deficient mice also deficient for aP2 showed protection from **atherosclerosis** in the absence of significant differences in serum lipids or insulin sensitivity. aP2-deficient macrophages showed alterations in inflammatory cytokine production and a reduced ability to accumulate cholesterol esters when exposed to modified lipoproteins. Apoe-/- mice with Ap2+/+ **adipocytes** and Ap2-/- macrophages generated by bone-marrow transplantation showed a comparable reduction in **atherosclerotic** lesions to those with total aP2 deficiency, indicating an independent role for macrophage aP2 in atherogenesis. Through its distinct actions in **adipocytes** and macrophages, aP2 provides a link between features of the metabolic syndrome and could be a new therapeutic target for the prevention of **atherosclerosis**.

7/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10242702 99355592 PMID: 10425206
PPARgamma activation induces the expression of the **adipocyte fatty acid binding protein** gene in human monocytes.
Pelton PD; Zhou L; Demarest KT; Burris TP
Endocrine Therapeutics, R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, 08869, USA.
Biochemical and biophysical research communications (UNITED STATES) Aug 2 1999, 261 (2) p456-8, ISSN 0006-291X Journal Code: 9Y8

Languages: ENGLISH
Document type: Journal [redacted]ticle
Record type: Completed

The peroxisome-proliferator activated receptor gamma (PPARgamma), a member of the nuclear receptor superfamily of ligand activated transcription factors, plays a key role in the anti-diabetic actions of the thiazolidinediones (TZDs). PPARgamma induces the expression of many genes involved in lipid anabolism, including the **adipocyte fatty acid binding protein** (aP2), and is a key regulator of **adipocyte** differentiation. PPARgamma is also expressed in hematopoietic cells and is up-regulated in activated monocytes/macrophages. Activation of PPARgamma may play a role in the induction of differentiation of macrophages to foam cells that are associated with **atherosclerotic** lesions. We report that both natural and synthetic PPARgamma agonists induce time- and dose-dependent increases in aP2 mRNA in both primary human monocytes and the monocytic cell line, THP-1. These data suggest that PPARgamma activation may play a role in monocyte differentiation and function analogous to its well-characterized role in **adipocytes**.

7/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09920723 98367366 PMID: 9702044
[Lipid metabolism related nuclear receptor--the structure, function, expression and classification of peroxisome proliferation-activated receptor (PPAR)]
Kawada T
Div. of Applied Life Sciences, Graduate School of Agric, Kyoto University.
Nippon rinsho (JAPAN) Jul 1998, 56 (7) p1722-8, ISSN 0047-1852
Journal Code: KIM
Languages: JAPANESE
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed

Peroxisome proliferator-activated receptors (PPARs) belongs to the nuclear hormone receptor superfamily. So far three different subtypes of PPAR (alpha, gamma, and delta (beta)) have been identified in amphibians, chicken, rodents and man. These receptors are transcription factors that control the beta-oxidation and transport pathways of **fatty** acids and **adipocyte** differentiation containing **fatty acid** synthesis under the modification of PPAR activation with CBP and its analogs. Thus, PPARs play an important role in lipid metabolism. Furthermore, altered **fatty acid** levels are associated with obesity, diabetes, hypertension and **atherosclerosis** , so PPARs may serve as molecular sensors in these metabolic disorders.

7/3,AB/5 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12223803 BIOSIS NO.: 199900518652
P450-epoxygenase metabolites bind peroxisome proliferator activated receptors and regulate cell lipid metabolism.
AUTHOR: Wang Dao Wen(a); Chen Jin; Johson Eric F; Hsu Mei-Hui; Capdevila Jorge H
AUTHOR ADDRESS: (a)Vanderbilt Univ., Nashville, TN**USA
JOURNAL: Circulation 98 (17 SUPPL.):pI665 Oct. 27, 1998
CONFERENCE/MEETING: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998
SPONSOR: The American Heart Association
ISSN: 0009-7322
RECORD TYPE: Citation

LANGUAGE: English
1998
? ds

Set	Items	Description
S1	630	ADIPOCYT? AND FATTY AND ACID AND BINDING AND PROTEIN?
S2	1547	AFABP OR AP2
S3	2049	S1 OR S2
S4	590	S3 AND (INHIBIT? OR TREAT?)
S5	0	S4 AND ATHEROSCLEROSIS
S6	8	S1 AND ATHEROSCLERO?
S7	5	RD (unique items)

? s s2 and atherosclero?

	1547	S2
	88239	ATHEROSCLERO?
S8	9	S2 AND ATHEROSCLERO?

? rd

...completed examining records

S9	6	RD (unique items)

? t s9/3,ab/all

9/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11443532 21279103 PMID: 11385507
Lack of macrophage fatty-acid-binding protein **aP2** protects mice deficient in apolipoprotein E against **atherosclerosis**.
Makowski L; Boord JB; Maeda K; Babaev VR; Uysal KT; Morgan MA; Parker RA; Suttles J; Fazio S; Hotamisligil GS; Linton MF
Division of Biological Sciences and Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA.
Nature medicine (United States) Jun 2001, 7 (6) p699-705, ISSN 1078-8956 Journal Code: CG5
Contract/Grant No.: HL65405-01, HL, NHLBI; T32 DK7061, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The adipocyte fatty-acid-binding protein, **aP2**, has an important role in regulating systemic insulin resistance and lipid metabolism. Here we demonstrate that **aP2** is also expressed in macrophages, has a significant role in their biological responses and contributes to the development of **atherosclerosis** . Apolipoprotein E (ApoE)-deficient mice also deficient for **aP2** showed protection from **atherosclerosis** in the absence of significant differences in serum lipids or insulin sensitivity. **aP2** -deficient macrophages showed alterations in inflammatory cytokine production and a reduced ability to accumulate cholesterol esters when exposed to modified lipoproteins. Apoe-/- mice with **Ap2**+/+ adipocytes and **Ap2**-/- macrophages generated by bone-marrow transplantation showed a comparable reduction in **atherosclerotic** lesions to those with total **aP2** deficiency, indicating an independent role for macrophage **aP2** in atherogenesis. Through its distinct actions in adipocytes and macrophages, **aP2** provides a link between features of the metabolic syndrome and could be a new therapeutic target for the prevention of **atherosclerosis**.

9/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10614886 20261281 PMID: 10799317
Fenofibrate and rosiglitazone lower serum triglycerides with opposing

effects on body weight.
Chaput E; Saladin R; S[redacted]estre M; Edgar AD
Department of Metabolic Diseases, Laboratoire Fournier, 50, rue de Dijon, Daix, 21121, France.
Biochemical and biophysical research communications (UNITED STATES) May 10 2000, 271 (2) p445-50, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Activators of peroxisome proliferator activated receptors (PPARs) are effective drugs to improve the metabolic abnormalities linking hypertriglyceridemia to diabetes, hyperglycemia, insulin-resistance, and **atherosclerosis** . We compared the pharmacological profile of a PPARalpha activator, fenofibrate, and a PPARgamma activator, rosiglitazone, on serum parameters, target gene expression, and body weight gain in (fa/fa) fatty Zucker rats and db/db mice as well as their association in db/db mice. Fenofibrate faithfully modified the expression of PPARalpha responsive genes. Rosiglitazone increased adipose tissue **aP2** mRNA in both models while increasing liver acyl CoA oxidase mRNA in db/db mice but not in fatty Zucker rats. Both drugs lowered serum triglycerides yet rosiglitazone markedly increased body weight gain while fenofibrate decreased body weight gain in fatty Zucker rats. KRP 297, which has been reported to be a PPARalpha and gamma co-activator, also affected serum triglycerides and insulin in fatty Zucker rats although no change in body weight gain was noted. These results serve to clearly differentiate the metabolic finality of two distinct classes of drugs, as well as their corresponding nuclear receptors, having similar effects on serum triglycerides. Copyright 2000 Academic Press.

9/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10242702 99355592 PMID: 10425206
PPARgamma activation induces the expression of the adipocyte fatty acid binding protein gene in human monocytes.
Pelton PD; Zhou L; Demarest KT; Burris TP
Endocrine Therapeutics, R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, 08869, USA.
Biochemical and biophysical research communications (UNITED STATES) Aug. 2 1999, 261 (2) p456-8, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The peroxisome-proliferator activated receptor gamma (PPARgamma), a member of the nuclear receptor superfamily of ligand activated transcription factors, plays a key role in the anti-diabetic actions of the thiazolidinediones (TZDs). PPARgamma induces the expression of many genes involved in lipid anabolism, including the adipocyte fatty acid binding protein (**aP2**), and is a key regulator of adipocyte differentiation. PPARgamma is also expressed in hematopoietic cells and is up-regulated in activated monocytes/macrophages. Activation of PPARgamma may play a role in the induction of differentiation of macrophages to foam cells that are associated with **atherosclerotic** lesions. We report that both natural and synthetic PPARgamma agonists induce time- and dose-dependent increases in **aP2** mRNA in both primary human monocytes and the monocytic cell line, THP-1. These data suggest that PPARgamma activation may play a role in monocyte differentiation and function analogous to its well-characterized role in adipocytes. Copyright 1999 Academic Press.

9/3,AB/4 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13244309 BIOSIS NO.: 200100451458
Absence of adipocyte fat[redacted]acid binding protein prevents [redacted] development of accelerated **atherosclerosis** in hypercholesterolemic mice.
AUTHOR: Perrella Mark A(a); Pellacani Andrea; Layne Matthew D; Patel Anand; Zhao Dezheng; Schreiber Barbara M; Storch Judith; Feinberg Mark W; Hsieh Chung-Ming; Haber Edgar; Lee Mu-En
AUTHOR ADDRESS: (a)Program of Developmental Cardiovascular Biology, Brigham and Women's Hospital, 75 Francis St., Boston, MA, 02115: mperrella@rics.bwh.harvard.edu**USA
JOURNAL: FASEB Journal 15 (10):p1774-1776 August, 2001
MEDIUM: print
ISSN: 0892-6638
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

9/3,AB/5 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12861612 BIOSIS NO.: 200100068761
aP2 fatty acid binding protein expression by macrophages accelerates early **atherosclerotic** lesion formation in apo-E deficient mice.
AUTHOR: Boord Jeffrey B(a); Fazio Sergio(a); Uysal Kadir; Babaev Vladimir R ; Brown Abigail M; Makowski Liza; Maeda Kazuhisa; Hotamisligil Gokhan S; Linton Macrae F
AUTHOR ADDRESS: (a)Vanderbilt Univ, Nashville, TN**USA
JOURNAL: Circulation 102 (18 Supplement):pII230 October 31, 2000
MEDIUM: print
CONFERENCE/MEETING: Abstracts from Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

9/3,AB/6 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10774086 BIOSIS NO.: 199799395231
Importance of defined mutations in the LAL gene for the manifestation of CESD and WD and characterization of the LAL promoter.
AUTHOR: Aslanidis C; Ries S; Buechler C; Fehringer P; Schmitz G
AUTHOR ADDRESS: Inst. Clin. Chem. Lab. Med., Univ. Regensburg, 93042 Regensburg**Germany
JOURNAL: Molecular Biology of the Cell 7 (SUPPL.):p296A 1996
CONFERENCE/MEETING: Annual Meeting of the 6th International Congress on Cell Biology and the 36th American Society for Cell Biology San Francisco, California, USA December 7-11, 1996
ISSN: 1059-1524
RECORD TYPE: Citation
LANGUAGE: English
1996
? ds

Set	Items	Description
S1	630	ADIPOCYT? AND FATTY AND ACID AND BINDING AND PROTEIN?
S2	1547	AFABP OR AP2

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S3       2049   S1 OR S2
S4        590   S3 AND ([redacted]IBIT? OR TREAT?)
S5          0   S4 AND ATHEROSCLEROSIS
S6          8   S1 AND ATHEROSCLERO?
S7          5   RD (unique items)
S8          9   S2 AND ATHEROSCLERO?
S9          6   RD (unique items)
? s s4 and arter?

            590  S4
         841148  ARTER?
    S10       0  S4 AND ARTER?
? s atherosclerosis and arter?

          69037  ATHEROSCLEROSIS
         841148  ARTER?
    S11   35824  ATHEROSCLEROSIS AND ARTER?
? s s11 and afabp

          35824  S11
             20  AFABP
    S12       0  S11 AND AFABP
? s s11 and fatty? and acid? and bind? and protein?

Processing
          35824  S11
         241216  FATTY?
        2456959  ACID?
        1127094  BIND?
        2653575  PROTEIN?
    S13      27  S11 AND FATTY? AND ACID? AND BIND? AND PROTEIN?
? rd

...completed examining records
    S14      24  RD (unique items)
? t s14/3,ab/all


 14/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11598710   21373907   PMID: 11481226
   Absence of adipocyte fatty acid binding protein
 prevents the development of accelerated atherosclerosis in
hypercholesterolemic mice.
  Perrella MA; Pellacani A; Layne MD; Patel A; Zhao D; Schreiber BM; Storch
J; Feinberg MW; Hsieh CM; Haber E; Lee ME
  Program of Developmental Cardiovascular Biology, Cardiovascular Division,
and. Pulmonary and Critical Care Division, Brigham and Women's Hospital,
Boston, Massachusetts 02115, USA. mperrella@rics.bwh.harvard.edu
  FASEB journal (United States) Aug 2001, 15 (10) p1774-6, ISSN
0892-6638 Journal Code: FAS
  Languages: ENGLISH
  Document type: Journal Article
  Record type: Completed


 14/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11443532   21279103   PMID: 11385507
  Lack of macrophage fatty-acid-binding protein aP2
protects mice deficient in apolipoprotein E against atherosclerosis.
  Makowski L; Boord JB; Maeda K; Babaev VR; Uysal KT; Morgan MA; Parker RA;
Suttles J; Fazio S; Hotamisligil GS; Linton MF
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Division of Biological Sciences and Department of Nutrition, Harvard School of Public Health, [redacted]ston, Massachusetts, USA.
Nature medicine (United States) Jun 2001, 7 (6) p699-705, ISSN 1078-8956 Journal Code: CG5
Contract/Grant No.: HL65405-01, HL, NHLBI; T32 DK7061, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The adipocyte **fatty-acid-binding protein**, aP2, has an important role in regulating systemic insulin resistance and lipid metabolism. Here we demonstrate that aP2 is also expressed in macrophages, has a significant role in their biological responses and contributes to the development of **atherosclerosis** . Apolipoprotein E (ApoE)-deficient mice also deficient for aP2 showed protection from **atherosclerosis** in the absence of significant differences in serum lipids or insulin sensitivity. aP2-deficient macrophages showed alterations in inflammatory cytokine production and a reduced ability to accumulate cholesterol esters when exposed to modified lipoproteins. Apoe-/- mice with Ap2+/+ adipocytes and Ap2-/- macrophages generated by bone-marrow transplantation showed a comparable reduction in atherosclerotic lesions to those with total aP2 deficiency, indicating an independent role for macrophage aP2 in atherogenesis. Through its distinct actions in adipocytes and macrophages, aP2 provides a link between features of the metabolic syndrome and could be a new therapeutic target for the prevention of **atherosclerosis**.

14/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11339515 21255090 PMID: 11356390
Plasma vascular endothelial growth factor and its receptor Flt-1 in patients with hyperlipidemia and **atherosclerosis** and the effects of fluvastatin or fenofibrate.
Blann AD; Belgore FM; Constans J; Conri C; Lip GY
Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, United Kingdom. a.blann@bham.ac.uk
American journal of cardiology (United States) May 15 2001, 87 (10) p1160-3, ISSN 0002-9149 Journal Code: 3DQ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Increased vascular endothelial cell growth factor (VEGF) may be important in cardiovascular pathophysiology (perhaps relating to angiogenesis and collateral vessel development) and **binds** target endothelium via receptors such as Flt-1. We hypothesized that there would be increased levels of plasma VEGF and Flt-1 in patients with **atherosclerosis** and others with hyperlipidemia compared with controls, and a reduction in these factors with 3 months of lipid-lowering therapy. Twenty patients with uncomplicated hyperlipidemia but no **atherosclerosis**, 20 patients with hyperlipidemia plus clear **atherosclerosis**, and 40 matched controls were studied. Plasma VEGF was higher in patient groups than in healthy controls ($p < 0.01$), but Flt-1 was not significantly altered. After lipid-lowering therapy, patients with uncomplicated hyperlipidemia had significantly reduced total cholesterol and VEGF (all $p < 0.05$) but no significant change in Flt-1. Lack of a significant correlation between the von Willebrand factor and VEGF suggests the latter is unrelated to endothelial damage. Plasma VEGF that increases in patients with uncomplicated hyperlipidemia free of major underlying **atherosclerosis** and in patients with hyperlipidemia plus established **atherosclerosis** is reduced by successful lipid-lowering treatment. These findings may have implications for the pathophysiology and treatment of hyperlipidemia and **atherosclerosis** , and suggest an alternative mechanism (i.e., modulation of angiogenesis) by which lipid-lowering therapy may reduce cardiovascular events beyond lipid reduction alone.

14/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11076766 21155097 PMID: 11229885
Postprandial lipoproteins and **atherosclerosis**.
Yu KC; Cooper AD
Research Institute, Ames Building, Palo Alto Medical Foundation 795 El Camino Real, Palo Alto, CA 94301.
Frontiers in bioscience (United States) Mar 1 2001, 6 pD332-54, ISSN 1093-4715 Journal Code: CUE
Languages: ENGLISH
Document type: Journal Article
Record type: In Process
During the postprandial state, dietary lipid is transported from the intestine to peripheral tissues by plasma lipoproteins called chylomicrons. In the capillary beds of peripheral tissues, chylomicron triglycerides are lipolyzed by the enzyme, lipoprotein lipase, allowing the delivery of free **fatty acids** to the cells. As a result, this produces a new particle of smaller size and enriched with cholesteryl ester referred to as chylomicron remnants. These particles are rapidly removed from the blood primarily by the liver. The liver has a complex chylomicron remnant removal system which is comprised of a combination of different mechanisms that include the low-density-lipoprotein receptor (LDLR) and the LDLR-related-**protein** (LRP). Furthermore, it has been suggested that there is a sequestration component whereby chylomicron remnants **bind** to heparan sulfate proteoglycans (HSPG) and/or hepatic lipase; this is then followed by transport to one or both of the above receptors for hepatic uptake. Over the years, a major concern has arisen about the association of chylomicron remnants and coronary heart disease (CHD) in man. Slow removal of chylomicron remnants, as reflected by a prolonged postprandial state, is now commonly observed in patients with CHD and those that have abnormal lipid disorders such as hypertriglyceridemia, familial hypercholesterolemia, familial combined hyperlipidemia and non-insulin-dependent-diabetes-mellitus. The present review will focus on (a) the details of the metabolic pathway (exogenous pathway) that describes the two-step processing of postprandial lipoproteins, (b) the role of the liver, the receptors, and the importance of efficient removal of chylomicron remnants from the blood circulation, and (c) the potential atherogenic effects of chylomicron remnants on the **arterial** wall.

14/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10905315 20568530 PMID: 11116101
Fluvastatin upregulates inducible nitric oxide synthase expression in cytokine-stimulated vascular smooth muscle cells.
Chen H; Ikeda U; Shimpo M; Ikeda M; Minota S; Shimada K
Department of Cardiology, Jichi Medical School, and the Health Science Center, Utsunomiya University, Tochigi, Japan.
Hypertension (UNITED STATES) Dec 2000, 36 (6) p923-8, ISSN 1524-4563 Journal Code: DCZ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Nitric oxide (NO) production by inducible NO synthase (iNOS) may play an important role in the pathogenesis of **atherosclerosis**. Although fluvastatin has been shown to reduce progression of **atherosclerosis**, it is not known whether it regulates iNOS expression. We investigated the effects of fluvastatin on iNOS expression and subsequent NO synthesis in vascular smooth muscle cells (VSMCs) and the mechanism by which fluvastatin exerts its effects. Fluvastatin significantly increased interleukin-1ss (IL-1ss)-induced nitrite production by VSMCs in a time-dependent (0 to 24 hours) and dose-dependent (10(-)(8) to 10(-)(5) mol/L) manner. Increased

nitrite production by fluvastatin was accompanied by increased iNOS mRNA and **protein** accumulation. IL-1ss induced nuclear factor-kappaB activation in VSMCs, which was not affected by fluvastatin. Exogenous mevalonate significantly prevented the stimulatory effect of fluvastatin on nitrite production. Cotreatment with geranylgeranyl-pyrophosphate also reversed the effect of fluvastatin. Furthermore, both Rho inhibitor C3 exoenzyme and Rho kinase inhibitor Y-27632 significantly increased IL-1ss-induced nitrite accumulation in VSMCs. These results demonstrated that fluvastatin upregulates iNOS expression and subsequent NO formation in rat VSMCs through inhibition of Rho.

14/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10868966 20455349 PMID: 10998459
Intestinal **fatty acid binding protein** polymorphism at codon 54 is not associated with postprandial responses to fat and glucose tolerance tests in healthy young Europeans. Results from EARS II participants.
Tahvanainen E; Molin M; Vainio S; Tiret L; Nicaud V; Farinaro E; Masana L ; Ehnholm C
Department of Biochemistry, National Public Health Institute, Mannerheimintie 166, 00300, Helsinki, Finland. esa tahvanainen@merck.com
Atherosclerosis (IRELAND) Oct 2000, 152 (2) p317-25, ISSN 0021-9150 Journal Code: 95X
Languages: ENGLISH
Document type: Journal Article; Multicenter Study
Record type: Completed
Polymorphism Ala54Thr of the intestinal **fatty acid-binding protein** 2 (FABP2) has been reported to have an effect on the **protein**'s affinity for long chain **fatty acids** and to be associated with serum lipid and insulin levels in fasting and especially postprandial states. We wanted to test whether this genetic variation is associated with fasting and postprandial glucose, insulin or lipid levels in 666 male university students participating in the second European **Atherosclerosis** Study (EARS II). We also studied whether the subgroup of 330 students with paternal history of myocardial infarction (MI) before the age of 55 have different genotype distribution than 336 matched controls. RESULTS: No difference in genotype distribution was observed between offspring with and without paternal history of MI or between populations from 11 European countries. The frequency of the threonine encoding allele was 0.276 in cases and 0.266 in controls. There were no differences in fasting or postprandial serum lipid, glucose or insulin levels between subjects having different genotypes. CONCLUSIONS: In this study FABP2 Ala54Thr polymorphism was not associated with lipid or glucose metabolism. In addition to environmental and genetic factors, selection of study population also may explain the difference between this and earlier studies.

14/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10820902 20464916 PMID: 11007963
Role of the peroxisome proliferator-activated receptors (PPAR) in **atherosclerosis**.
Neve BP; Fruchart JC; Staels B
Departement d'Atherosclerose, U.325 INSERM, Institut Pasteur de Lille, France.
Biochemical pharmacology (ENGLAND) Oct 15 2000, 60 (8) p1245-50, ISSN 0006-2952 Journal Code: 9Z4
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed

Peroxisome proliferator-activated receptors (PPAR) are ligand-activated transcription factors which form a subfamily of the nuclear receptor gene family. PPAR activators have effects on both metabolic risk factors and on vascular inflammation related to **atherosclerosis**. PPAR have profound effects on the metabolism of lipoproteins and **fatty acids**. PPAR alpha **binds** hypolipidemic fibrates, whereas PPAR gamma has a high affinity for antidiabetic glitazones. Both PPAR are activated by **fatty acids** and their derivatives. Activation of PPAR alpha increases the catabolism of **fatty acids** at several levels. In the liver, it increases uptake of **fatty acids** and activates their beta-oxidation. The effects that PPAR alpha exerts on triglyceride-rich lipoproteins is due to their stimulation of lipoprotein lipase and repression of apolipoprotein CIII expression, while the effects on high-density lipoproteins depend upon the regulation of apolipoproteins AI and AII. PPAR gamma has profound effects on the differentiation and function of adipose tissue, where it is highly expressed. PPAR are also expressed in atherosclerotic lesions. PPAR are present in vascular endothelial cells, smooth muscle cells, monocytes, and monocyte-derived macrophages. Via negative regulation of nuclear factor-kappa B and activator **protein** -1 signalling pathways, PPAR alpha inhibits expression of inflammatory genes, such as interleukin-6, cyclooxygenase-2, and endothelin-1. Furthermore, PPAR alpha inhibits expression of monocyte-recruiting **proteins** such as vascular cell adhesion molecule (VCAM)-1 and induces apoptosis in monocyte-derived macrophages. PPAR gamma activation in macrophages and foam cells inhibits the expression of activated genes such as inducible nitric oxide synthase, matrix metalloproteinase-9 and scavenger receptor A. PPAR gamma may also affect the recruitment of monocytes in atherosclerotic lesions as it is involved in the expression of VCAM-1 and intracellular adhesion molecule-1 in vascular endothelial cells. The involvement of PPAR in **atherosclerosis** , a disease with a chronic inflammatory character, suggests that they may play a role in other inflammatory-related diseases as well.

14/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10808446 99408498 PMID: 10480621
Variants of the insulin receptor substrate-1 and **fatty acid binding protein** 2 genes and the risk of type 2 diabetes, obesity, and hyperinsulinemia in African-Americans: the **Atherosclerosis** Risk in Communities Study.
Lei HH; Coresh J; Shuldiner AR; Boerwinkle E; Brancati FL
Department of Epidemiology, the Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland, USA.
Diabetes (UNITED STATES) Sep 1999, 48 (9) p1868-72, ISSN 0012-1797 Journal Code: E8X
Contract/Grant No.: N01-HC-55015, HC, NHLBI; N01-HC-55016, HC, NHLBI; N01-HC-55018, HC, NHLBI; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We conducted a community-based case-control study of African-American men and women in the **Atherosclerosis** Risk in Communities Study. The allele frequencies of the Gly972Arg variant of the insulin receptor substrate-1 (IRS-1) gene and the Ala54Thr variant of the **fatty acid binding protein** 2 (FABP2) gene were compared in 992 normal control subjects and three patient groups: 1) 321 type 2 diabetic individuals, 2) 260 severely obese individuals, and 3) 258 markedly hyperinsulinemic individuals without diabetes. Allele frequencies of Gly972Arg IRS-1 and Ala54Thr FABP2 were 0.07 and 0.22, respectively; there were no differences in allele or genotype frequencies between patients and control subjects for either gene variant. In weighted linear regression of all patients and control subjects, the presence of the IRS-1 gene variant

was associated with a 0.85 (0.42) kg/m2 higher BMI (P = 0.04). In addition, individuals with at least one IRS-1 Arg972 allele and two FABP2 Thr54 alleles had a BMI of 33.3 (7.9) kg/m2, compared with 30.0 (6.3) kg/m2 for those with neither allele (P = 0.05). These results suggest that in African-Americans, these variants in the IRS-1 and FABP2 genes are not associated with the risk of type 2 diabetes, severe obesity, or marked hyperinsulinemia, but that their independent and joint effects may be associated with small increases in BMI.

14/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10808005 99360344 PMID: 10431661
Peroxisome proliferator-activated receptor-alpha activators regulate genes governing lipoprotein metabolism, vascular inflammation and **atherosclerosis**.
Fruchart JC; Duriez P; Staels B
Department of Atherosclerosis, INSERM U325, Pasteur Institute, University of Lille II, France. Jean-Charles.Fruchart@pasteur-lille.fr
Current opinion in lipidology (ENGLAND) Jun 1999, 10 (3) p245-57, ISSN 0957-9672 Journal Code: B05
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
The peroxisome proliferator-activated receptors (PPARs) [alpha, delta (beta) and gamma] form a subfamily of the nuclear receptor gene family. All PPARs are, albeit to different extents, activated by **fatty acids** and derivatives; PPAR-alpha **binds** the hypolipidemic fibrates whereas antidiabetic glitazones are ligands for PPAR-gamma. PPAR-alpha activation mediates pleiotropic effects such as stimulation of lipid oxidation, alteration in lipoprotein metabolism and inhibition of vascular inflammation. PPAR-alpha activators increase hepatic uptake and the esterification of free **fatty acids** by stimulating the **fatty acid** transport **protein** and acyl-CoA synthetase expression. In skeletal muscle and heart, PPAR-alpha increases mitochondrial free **fatty acid** uptake and the resulting free **fatty acid** oxidation through stimulating the muscle-type carnitine palmitoyltransferase-I. The effect of fibrates on the metabolism of triglyceride-rich lipoproteins is due to a PPAR-alpha dependent stimulation of lipoprotein lipase and an inhibition of apolipoprotein C-III expressions, whereas the increase in plasma HDL cholesterol depends on an overexpression of apolipoprotein A-I and apolipoprotein A-II. PPARs are also expressed in atherosclerotic lesions. PPAR-alpha is present in endothelial and smooth muscle cells, monocytes and monocyte-derived macrophages. It inhibits inducible nitric oxide synthase in macrophages and prevents the IL-1-induced expression of IL-6 and cyclooxygenase-2, as well as thrombin-induced endothelin-1 expression, as a result of a negative transcriptional regulation of the nuclear factor-kappa B and activator **protein**-1 signalling pathways. PPAR activation also induces apoptosis in human monocyte-derived macrophages most likely through inhibition of nuclear factor-kappa B activity. Therefore, the pleiotropic effects of PPAR-alpha activators on the plasma lipid profile and vascular wall inflammation certainly participate in the inhibition of **atherosclerosis** development observed in angiographically documented intervention trials with fibrates.

14/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10803571 99257364 PMID: 10323782
Role of group II secretory phospholipase A2 in **atherosclerosis**: 2. Potential involvement of biologically active oxidized phospholipids.
Leitinger N; Watson AD; Hama SY; Ivandic B; Qiao JH; Huber J; Faull KF;

Grass DS; Navab M; Fogelman AM; de Beer FC; Lusis AJ; Berliner JA
Department of Medicine, University of California, Los Angeles, USA.
Arteriosclerosis, thrombosis, and vascular biology (UNITED STATES) May 1999, 19 (5) p1291-8, ISSN 1079-5642 Journal Code: B89
Contract/Grant No.: AG10886, AG, NIA; HL30568, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Secretory nonpancreatic phospholipase A2 (group II sPLA2) is induced in inflammation and present in atherosclerotic lesions. In an accompanying publication we demonstrate that transgenic mice expressing group II sPLA2 developed severe **atherosclerosis**. The current study was undertaken to determine whether 1 mechanism by which group II sPLA2 might contribute to the progression of inflammation and **atherosclerosis** is by increasing the formation of biologically active oxidized phospholipids. In vivo measurements of bioactive lipids were performed, and in vitro studies tested the hypothesis that sPLA2 can increase the accumulation of bioactive phospholipids. We have shown previously that 3 oxidized phospholipids derived from the oxidation of 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (PAPC) stimulated endothelial cells to **bind** monocytes, a process that is known to be an important step in atherogenesis. We now show that these 3 biologically active phospholipids are significantly increased in livers of sPLA2 transgenic mice fed a high-fat diet as compared with nontransgenic littermates. We present in vitro evidence for several mechanisms by which these phospholipids may be increased in sPLA2 transgenics. These studies demonstrated that polyunsaturated free **fatty acids**, which are liberated by sPLA2, increased the formation of bioactive phospholipids in LDL, resulting in increased ability to stimulate monocyte-endothelial interactions. Moreover, sPLA2-treated LDL was oxidized by cocultures of human aortic endothelial cells and smooth muscle cells more efficiently than untreated LDL. Analysis by electrospray ionization-mass spectrometry revealed that the bioactive phospholipids, compared with unoxidized PAPC, were less susceptible to hydrolysis by human recombinant group II sPLA2. In addition, HDL from the transgenic mice and human HDL treated with recombinant sPLA2 in vitro failed, in the coculture system, to protect against the formation of biologically active phospholipids in LDL. This lack of protection may in part relate to the decreased levels of paraoxonase seen in the HDL isolated from the transgenic animals. Taken together, these studies show that levels of biologically active oxidized phospholipids are increased in sPLA2 transgenic mice; they also suggest that this increase may be mediated by effects of sPLA2 on both LDL and HDL.

14/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10774057 20144293 PMID: 10680041
Regulation of macrophage gene expression by peroxisome-proliferator-activated receptor gamma: implications for cardiovascular disease.
Tontonoz P; Nagy L
Department of Pathology, University of California, Los Angeles 90095, USA. ptontonoz@mednet.ucla.edu
Current opinion in lipidology (ENGLAND) Dec 1999, 10 (6) p485-90, ISSN 0957-9672 Journal Code: B05
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed

The peroxisome-proliferator-activated receptor gamma is a member of the nuclear receptor superfamily that functions as a key transcriptional regulator of cell differentiation and lipid metabolism. In addition, peroxisome-proliferator-activated receptor gamma is now recognized to be the biological receptor for the thiazolidinedione class of antidiabetic drugs, which includes troglitazone and rosiglitazone. Recent evidence indicates that peroxisome-proliferator-activated receptor gamma is

expressed at high levels in macrophages, including the foam cells of atherosclerotic lesions. Oxidized low-density lipoprotein, which plays a central role in lesion development, can activate peroxisome-proliferator-activated receptor gamma by providing the cell with oxidized **fatty acid** ligands of the receptor. The elucidation of a peroxisome-proliferator-activated receptor gamma signalling pathway in macrophages provides a mechanism by which oxidized lipids may directly regulate gene expression in the context of the atherosclerotic lesions. A number of potential target genes for peroxisome-proliferator-activated receptor gamma in these cells have been identified. Some, such as the type B scavenger receptor CD36 are induced by peroxisome-proliferator-activated receptor gamma ligands, whereas others, such as scavenger receptor type A, inducible nitric oxide synthetase and certain cytokines, are repressed. Given the widespread clinical use of thiazolidinediones, it is important to consider the influence of these drugs on the risk of **atherosclerosis**. The net effect of peroxisome-proliferator-activated receptor gamma ligands on the atherogenic process is likely to reflect a balance between local effects in the **artery** wall and systemic effects on lipid metabolism.

14/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10748308 98226736 PMID: 9560197

Protein-bound acrolein: potential markers for oxidative stress.

Uchida K; Kanematsu M; Sakai K; Matsuda T; Hattori N; Mizuno Y; Suzuki D; Miyata T; Noguchi N; Niki E; Osawa T

Laboratory of Food and Biodynamics, Nagoya University Graduate School of Bioagricultural Sciences, Nagoya 464-8601, Japan. uchidak@agr.nagoya-u.ac.jp

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Apr 28 1998, 95 (9) p4882-7, ISSN 0027-8424
Journal Code: PV3

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Acrolein (CH2==CH---CHO) is known as a ubiquitous pollutant in the environment. Here we show that this notorious aldehyde is not just a pollutant, but also a lipid peroxidation product that could be ubiquitously generated in biological systems. Upon incubation with BSA, acrolein was rapidly incorporated into the **protein** and generated the **protein**-linked carbonyl derivative, a putative marker of oxidatively modified **proteins** under oxidative stress. To verify the presence of **protein**-bound acrolein in vivo, the mAb (mAb5F6) against the acrolein-modified keyhole limpet hemocyanin was raised. It was found that the acrolein-lysine adduct, Nepsilon-(3-formyl-3, 4-dehydropiperidino)lysine, constitutes an epitope of the antibody. Immunohistochemical analysis of atherosclerotic lesions from a human aorta demonstrated that antigenic materials recognized by mAb5F6 indeed constituted the lesions, in which intense positivity was associated primarily with macrophage-derived foam cells and the thickening neointima of **arterial** walls. The observations that (i) oxidative modification of low-density lipoprotein with Cu2+ generated the acrolein-low-density lipoprotein adducts and (ii) the iron-catalyzed oxidation of arachidonate in the presence of **protein** resulted in the formation of antigenic materials suggested that polyunsaturated **fatty acids** are sources of acrolein that cause the production of **protein**-bound acrolein. These data suggest that the **protein**-bound acrolein represents potential markers of oxidative stress and long-term damage to **protein** in aging, **atherosclerosis**, and diabetes.

14/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10743800 98102597 PMID: 9439479
Metabolism of native and naturally occurring multiple modified low density lipoprotein in smooth muscle cells of human aortic intima.
Tertov VV; Orekhov AN
Institute of Experimental Cardiology, Cardiology Research Center, Moscow, Russia.
Experimental and molecular pathology (UNITED STATES) 1997, 64 (3) p127-45, ISSN 0014-4800 Journal Code: EQ5
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The subfraction of low density lipoprotein (LDL) with low sialic **acid** content that caused accumulation of cholesterol esters in human aortic smooth muscle cells has been found in the blood of coronary **atherosclerosis** patients. It was demonstrated that this subfraction consists of LDL with small size, high electronegative charge, reduced lipid content, altered tertiary structure of apolipoprotein B, etc. LDL of this subfraction is naturally occurring multiple-modified LDL (nomLDL). In this study we compared the **binding**, uptake and proteolytic degradation of native LDL and nomLDL by smooth muscle cells cultured from human grossly normal intima, **fatty** streaks, and atherosclerotic plaques. Uptake of nomLDL by normal and atherosclerotic cells was 3.5- and 6-fold, respectively, higher than uptake of native LDL. Increased uptake of nomLDL was due to increased **binding** of this LDL by intimal smooth muscle cells. The enhanced **binding** is explained by the interaction of nomLDL with cellular receptors other than LDL-receptor. Modified LDL interacted with the scavenger receptor, asialoglycoprotein receptor, and also with cell surface proteoglycans. Rates of degradation of nomLDL were 1.5- and 5-fold lower than degradation of native LDL by normal and atherosclerotic cells, respectively. A low rate of nomLDL degradation was also demonstrated in homogenates of intimal cells. Activities of lysosomal **proteinases** of atherosclerotic cells were decreased compared with normal cells. Pepstatin A, a cathepsin D inhibitor, completely inhibited lipoprotein degradation, while serine, thiol, or metallo-**proteinase** inhibitors had partial effect. This fact reveals that cathepsin D is involved in initial stages of apoB degradation by intimal smooth muscle cells. Obtained data show that increased uptake and decreased lysosomal degradation of nomLDL may be the main cause of LDL accumulation in human aortic smooth muscle cells, leading to foam cell formation.

14/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10452302 20084754 PMID: 10617950
Zinc protects against apoptosis of endothelial cells induced by linoleic **acid** and tumor necrosis factor alpha.
Meerarani P; Ramadass P; Toborek M; Bauer HC; Bauer H; Hennig B
Departments of Nutrition and Food Science and Surgery, University of Kentucky, Lexington, and the Molecular Biology Institute, Austrian Academy of Sciences, Salzburg.
American journal of clinical nutrition (UNITED STATES) Jan 2000, 71 (1) p81-7, ISSN 0002-9165 Journal Code: 3EY
Contract/Grant No.: 1 P42 ES 07380, ES, NIEHS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
BACKGROUND: Zinc requirements of the vascular endothelium may be increased in inflammatory conditions, ie, **atherosclerosis**, in which apoptotic cell death is prevalent. OBJECTIVE: We hypothesized that zinc deficiency may potentiate disruption of endothelial cell integrity mediated by **fatty acids** and inflammatory cytokines by enhancing pathways that lead to apoptosis and up-regulation of caspase genes. DESIGN: Endothelial cells were maintained in low-serum medium or grown in culture media containing selected chelators, ie, diethylenetriaminepentaacetate or

N,N,N', N'-tetrakis(2-pyridylmethyl)-ethylenediamine (TPEN), with or without zinc supplementation. Subsequently, cells were treated with linoleic **acid** , tumor necrosis factor alpha (TNF-alpha), or both. We studied the effect of zinc deficiency and supplementation on the induction of apoptosis by measuring caspase-3 activity, cell **binding** of annexin V, and DNA fragmentation. RESULTS: Our results indicated that linoleic **acid** and TNF-alpha independently, but more markedly in concert, up-regulated caspase-3 activity and induced annexin V **binding** and DNA fragmentation. Zinc deficiency, especially when induced by TPEN, dramatically increased apoptotic cell death induced by cytokines and lipids compared with control cultures. Supplementation of low-serum- or chelator-treated endothelial cells with physiologic amounts of zinc caused a marked attenuation of apoptosis induced by linoleic **acid** and TNF-alpha. Morphologic changes of cells observed during zinc deficiency were prevented by zinc supplementation. Media supplementation with other divalent cations (eg, calcium and magnesium) did not mimic the protective role of zinc against apoptosis. CONCLUSIONS: Our data indicate that zinc is vital to vascular endothelial cell integrity, possibly by regulating signaling events to inhibit apoptotic cell death.

14/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09529368 97312342 PMID: 9168783
Induction of P-selectin by oxidized lipoproteins. Separate effects on synthesis and surface expression.
Vora DK; Fang ZT; Liva SM; Tyner TR; Parhami F; Watson AD; Drake TA; Territo MC; Berliner JA
Department of Medicine, University of California, Los Angeles 90024, USA.
Circulation research (UNITED STATES) Jun 1997, 80 (6) p810-8, ISSN 0009-7330 Journal Code: DAJ
Contract/Grant No.: HL-07412, HL, NHLBI; HL-30568, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Leukocyte **binding** to the endothelium is one of the earliest events in the occurrence of **atherosclerosis**. Leukocyte adhesion molecules involved in this process have not been definitely identified. We have found that treatment of human aortic endothelial cells (HAECs) with minimally modified low-density lipoprotein (MM-LDL) for 24 hours caused a 2- to 3-fold increase of P-selectin **protein** , with little change in P-selectin surface expression. A 15-minute histamine treatment of cells exposed to MM-LDL caused a 50% to 100% increase in P-selectin surface expression compared with cells not treated with the lipoprotein. This increase resulted in a 2-fold increase in **binding** of leukocytes to the endothelium. Immunostaining of permeabilized HAECs after MM-LDL treatment also revealed a highly reproducible increase in intracellular P-selectin associated with rod-shaped structures, typical of Weibel-Palade bodies. Oxidized phospholipids were shown to be mainly responsible for the action of MM-LDL. This increased P-selectin expression was associated with MM-LDL-induced cAMP elevation. Like histamine, highly oxidized low-density lipoprotein, especially the oxidized **fatty acids** , caused immediate redistribution of P-selectin to the cell surface followed by reinternalization. Immunohistochemical staining showed that endothelial cells on human **fatty** streak lesions expressed increased levels of P-selectin compared with nonlesion areas. These studies suggest that P-selectin may play an important role in early recruitment of mononuclear cells to the subendothelium in human **atherosclerosis** and that oxidized lipoproteins may contribute to the increased expression of this molecule by increasing intracellular stores and causing redistribution to the cell surface.

14/3,AB/16 (Item 16 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09520232 97017635 PMID: 8864252
Relation of C4b-**binding protein** to athero-sclerosis of the descending thoracic aorta.
Kimoto K; Inoue T; Oku K; Mori T; Kusuda M; Handa K; Sakata N; Sasaki J; Arakawa K
Department of Internal Medicine, School of Medicine, Fukuoka University, Japan.
Artery (UNITED STATES) 1996, 22 (2) p101-14, ISSN 0098-6127 Journal Code: 8NN
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
C4b **binding protein** (C4bp) is a regulator of the classical pathway of the complementing system. It forms a complex with **protein** S which serves as a cofactor of coagulation inhibitor, **protein** C. We have reported that C4bp is an acute phase reactant and associated with total cholesterol and triglyceride concentrations (Biochim. Biophys. Acta 963 (1988) 98-108). This suggests a possible association of C4bp with athero-sclerosis. We examined the relation of C4bp levels and the severity of **atherosclerosis** of the descending thoracic aorta in 98 Japanese men. The severity of aortic **atherosclerosis** was assessed by average sclerotic length (ASL) and average sclerotic area (ASA), using transesophageal echocardiography. After adjustment for age, C4bp levels increased significantly with increasing ASL and ASA. The association remained significant even after adjusting for total cholesterol, hypertension, smoking, drinking, body mass index, fasting blood sugar, and uric **acid** . Immunohistochemical analysis of specimens of the descending thoracic aorta from autopsies, demonstrated the presence of C4bp in the foamy macrophages of **fatty** streaks and the necrotic core of atheromatous plaque. These findings indicate that the serum level of C4bp can serve as an independent indicator of aortic athero-sclerosis.

14/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08740495 95408292 PMID: 7677772
Apolipoprotein B-bound lipids as a marker for evaluation of low density lipoprotein oxidation in vivo.
Tertov VV; Kaplun VV; Dvoryantsev SN; Orekhov AN
Institute of Experimental Cardiology, Russian Academy of Science, Moscow.
Biochemical and biophysical research communications (UNITED STATES) Sep 14 1995, 214 (2) p608-13, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
It has been generally accepted that oxidized low density lipoprotein (LDL) plays an important role in atherogenesis. However, oxidized LDL was not detected in patients' blood and the extent of LDL oxidation in vivo is unknown. We have suggested that LDL oxidation may lead to a formation of covalent links between lipids and apolipoprotein B. LDL were oxidized by copper ions, 2,2'-azobis-(2-aminopropane hydrochloride), sodium hypochlorite or by incubation with macrophages. Oxidized LDL were delipidated by repeated extraction with organic solvents. After mild alkaline hydrolysis **protein** -bound sterols were identified colorimetrically and by high-performance liquid chromatography. **Protein**-bound phospholipid residues were detected by nuclear magnetic resonance and colorimetric determination of phosphate. Using radiolabeled lipids it was also shown that free and esterified cholesterol, phospholipids, as well as triglyceride and free **fatty acid** residues can form covalent bonds with apolipoprotein B. The ability of lipids to **bind** to apolipoprotein B correlates with the degree of unsaturation of their **fatty acids** and depends on the nature of

polar head of phospholipids. When LDL were oxidized with copper ions, the content of **protein** -bound lipids increased gradually up to 24 h of incubation, while the levels of conjugated dienes, hydroperoxides and thiobarbituric **acid** -reactive substances changed in varying manners. It has been demonstrated that the content of **protein**-bound sterols in multiple-modified desialylated LDL of patients with coronary **atherosclerosis** is higher than that in native LDL. Our results suggest that the level of **protein**-bound lipids may be a marker of LDL oxidation and can be used to evaluate the association of lipoprotein oxidation and atherogenesis.

14/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08067885 91070963 PMID: 2253471
Arterial fatty acid-binding protein activity associated with dietarily-induced and spontaneously occurring **atherosclerosis** in the rabbit (Oryctolagus cuniculus).
St John LC; Bell FP
Metabolic Diseases Research, Upjohn Company, Kalamazoo, MI 49001.
Comparative biochemistry and physiology (ENGLAND) 1990, 97 (1) p123-7, ISSN 0305-0491 Journal Code: DNV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. Adult WHHL rabbits, or New Zealand rabbits fed either a stock chow diet or a high cholesterol diet were evaluated to assess the relationship between the development of aortic **atherosclerosis** and **arterial** FABP activity. 2. Aortic FABP activity was significantly (P less than 0.05) lower in atherosclerotic New Zealand aortas (0.039 +/- 0.008 nmol palmitoyl CoA bound/mg soluble prot) which had developed macroscopic lesions on 80% of the aortic surface as compared to lesion-free New Zealand aortas (0.053 +/- 0.002 nmol palmitoyl CoA bound/mg soluble prot). 3. In spontaneously hyperlipidemic rabbit (WHHL) aortas, FABP activity (0.023 +/- 0.004 nmol palmitoyl CoA bound/mg soluble prot) was significantly lower (P less than 0.05) than in either the normal or atherosclerotic New Zealand aortas. 4. To our knowledge, this study is the first to report a change in **arterial** FABP with the atherogenic process.

14/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07184857 92370947 PMID: 1354584
Temporal evaluation of **fatty acid-binding protein** (FABP) activity in association with the development of **atherosclerosis** in the rabbit.
St John LC; Bell FP
Upjohn Laboratories, Upjohn Company, Kalamazoo, MI 49001.
Comparative biochemistry and physiology (ENGLAND) Jun 1992, 102 (2) p357-61, Journal Code: B59
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. The relationship between **atherosclerosis** development and changes in **arterial fatty acid binding protein** (FABP) activity was investigated in the aortas of New Zealand rabbits which were fed an atherogenic diet containing 1% cholesterol and 3% peanut oil for 16 weeks. 2. At 4-week intervals, FABP activity, cholesterol and microsomal acylCoA:cholesterol acyltransferase (ACAT) activity were determined in aortic tissue and serum cholesterol was measured; age-matched normal rabbits served as control comparators. 3. Serum cholesterol increased from 35 mg/dl in the normal rabbits to 2290 mg/dl in the 16-week cholesterol-fed rabbits. 4. The microsomal fraction isolated from cholesterol-fed rabbit

aortas exhibited a progressive elevation in ACAT activity as time on the diet increased. By 12 weeks, ACAT activity had increased approximately 10-fold relative to normal activity. 5. **Arterial** cholesterol content of the cholesterol-fed animals increased from less than 2 mg/g wet weight to greater than 10 mg/g wet weight at 12 and 16 weeks. In contrast, **arterial** FABP activity gradually decreased with time on the cholesterol diet; a significant decrease (P less than 0.05) was observed at 16 weeks, where palmitoyl CoA **binding** was decreased from 61.0 to 36.3 pmol/mg **protein**. 6. In the cholesterol-fed rabbits, total **arterial** cholesterol and ACAT activity showed a significant (P less than 0.05) inverse correlation to FABP activity with correlation coefficients of -0.93 and -0.95, respectively. 7. Additionally, FABP activity increased significantly (P less than 0.05) in the 16-week normal rabbit as compared to the 4-week normal rabbit, suggesting an age-dependent interaction.

14/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07171171 92092617 PMID: 1753684
Lipid changes in the nephrotic syndrome: new insights into pathomechanisms and treatment.
D'Amico G
Divisone di Nefrologia e Dialisi, Ospedale S. Carlo Borromeo, Milano.
Klinische Wochenschrift (GERMANY) Sep 3 1991, 69 (13) p618-22,
ISSN 0023-2173 Journal Code: KWH
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
The abnormalities of lipid metabolism in nephrotic syndrome consist in an increase in total and low-density lipoprotein (LDL) cholesterol, apolipoproteins B (ApoB), C-II and C-III, associated in patients with heavier or marked hypoalbuminemia with an increase in triglycerides and very low-density lipoprotein (VLDL) cholesterol, while the high-density lipoproteins (HDL) are distributed abnormally (increased HDL3 fraction and decreased HDL2 fraction) and the Apo A-I to Apo B ratio is reduced. Both increased hepatic lipoprotein synthesis and reduced removal capacity contribute to this hyperlipidemia. **Proteinuria** may lead to the lipoprotein abnormalities through stimulation of VLDL synthesis by the liver induced by hypoalbuminemia, although it has been more recently suggested that urinary **protein** loss is associated with the urinary loss of some important cofactor for the regulation of lipid synthesis or catabolism. Treatment of lipid abnormalities in patients with long-lasting heavy **proteinuria** is mandatory, because they may cause or contribute to accelerated **atherosclerosis** , but also because they appear to accelerate progression of renal disease by favouring mesangial sclerosis. Four groups of lipid-lowering drugs have been tested: 1) bile **acid-binding** resins; 2) fibric **acid**; 3) probucol; 4) inhibitors of HMG CoA reductase. The drugs of the last group appear to be effective and safe in short-term experiments, but long-term studies are necessary to confirm their validity. A dietary approach, consisting in a strictly vegetarian soy diet, very rich in poly- and monounsaturates **fatty acids** , has been recently tested by the author, with very promising results.

14/3,AB/21 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13081183 BIOSIS NO.: 200100288332
The cholesterol quartet.
AUTHOR: Goldstein Joseph L(a); Brown Michael S(a)
AUTHOR ADDRESS: (a)Department of Molecular Genetics, University of Texas

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JOURNAL: Science (Washington D C) 292 (5520):p1310-1312 18 May, 2001
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ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

14/3,AB/22 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12904474 BIOSIS NO.: 200100111623
HIV protease inhibitor-induced hyperlipidemia and lipodystrophy is mediated through regulation of sterol responsive element **binding protein** (SREBP) responsive genes.
AUTHOR: Kuhel David G(a); Woollett Laura A(a); Fichtenbaum Carl J(a); Hui David Y(a)
AUTHOR ADDRESS: (a)Univ of Cincinnati, Cincinnati, OH**USA
JOURNAL: Circulation 102 (18 Supplement):pII360 October 31, 2000
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LANGUAGE: English
SUMMARY LANGUAGE: English
2000

14/3,AB/23 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12537860 BIOSIS NO.: 200000291362
Dietary soy-derived isoflavone phytoestrogens: Could they have a role in coronary heart disease prevention?.
AUTHOR: Tikkanen Matti J; Adlercreutz Herman
AUTHOR ADDRESS: (a)Department of Medicine, Helsinki University Central Hospital, 00290, Helsinki**Finland
JOURNAL: Biochemical Pharmacology 60 (1):p1-5 July 1, 2000
MEDIUM: print.
ISSN: 0006-2952
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Soy **protein**-containing foods are a rich source of isoflavone phytoestrogens, such as genistein and daidzein. There is great interest in these substances, as lower rates of chronic diseases, including coronary heart disease, have been associated with high dietary intake of soy-containing foods. Soy phytoestrogens **bind** weakly to estrogen receptors, and some **bind** more strongly to estrogen receptor-beta compared with estrogen receptor-alpha. A meta-analysis has indicated that isoflavone phytoestrogens lowered plasma cholesterol concentrations in subjects with initially elevated levels, but had little effect in subjects with normal cholesterol concentrations. These substances reportedly may also have beneficial effects on **arterial** endothelial function. In addition to these potentially antiatherogenic effects, many laboratories are investigating other possible mechanisms,

including antioxidative and antiproliferative properties of these substances. We have shown that dietary supplementation with soy-derived isoflavones reduced the in vitro oxidation susceptibility of low-density lipoprotein (LDL). To further explore this phenomenon, we incorporated genistein and daidzein into LDL molecules in vitro with the aid of an artificial transfer system. However, it was necessary to convert the isoflavone molecules to fat-soluble derivatives, **fatty acid** esters (analogous to esterified endogenous estrogens, which are known to occur in vivo), to achieve significant incorporation. The LDLs containing esterified isoflavones were shown to be less susceptible to oxidation in vitro than native LDL. We also employed U937 cell cultures for investigating the effects of isoflavone-containing LDLs on cell proliferation. Some of these LDLs exhibited antiproliferative effects in cultured U937 cells. In summary, lipophilic phytoestrogen derivatives could be incorporated into LDLs, increasing their oxidation resistance and antiproliferative efficacy ex vivo, both of which are, in theory, antiatherogenic effects. Further studies are needed to assess to what extent analogous effects could be produced in vivo and whether such substances have a role in hormone replacement and coronary heart disease prevention in postmenopausal women.

2000

14/3,AB/24 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06811629 BIOSIS NO.: 000088121073
RECOGNITION OF OXIDIZED LOW DENSITY LIPOPROTEIN BY THE SCAVENGER RECEPTOR OF MACROPHAGES RESULTS FROM DERIVATIZATION OF APOLIPOPROTEIN B BY PRODUCTS OF **FATTY ACID** PEROXIDATION
AUTHOR: STEINBRECHER U P; LOUGHEED M; KWAN W-C; DIRKS M
AUTHOR ADDRESS: DIV. GASTROENTEROL., DEP. MED., UNIV. BRITISH COLUMBIA, VANCOUVER, BRITISH COLUMBIA V6T 1W5, CANADA.
JOURNAL: J BIOL CHEM 264 (26). 1989. 15216-15223. 1989
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Uptake of cholesterol-containing lipoproteins by macrophages in the **arterial** intima is believed to be an important step in the pathogenesis of **atherosclerosis**. There are a number of possible mechanisms by which macrophages might accumulate cholesterol, and one that has attracted much interest recently involves the uptake of oxidatively modified low density lipoprotein (LDL) via a specific cell surface receptor, termed the scavenger or acetyl-LDL receptor. Previous studies have shown that chemical derivatization of LDL with reagents that result in neutralization of the charge of lysine amino groups also allows recognition by this receptor. As well, it has been shown tht oxidation of LDL is accompanied by a decrease in free lysine groups and **binding** of lipid products to apolipoprotein B. The present studies were done to further characterize the receptor-**binding** domain on oxidized LDL. It was found that LDL could be modified by incubation with water-soluble products derived from autoxidized unsaturated **fatty acids** under conditions that inhibited oxidation of the LDL itself. The LDL modified in this way had increased electrophoretic mobility but showed no evidence of the oxidative damage that typifies LDL oxidized by exposure to metal ions. Furthermore, the oxidation product-modified LDL was rapidly degraded by cultured macrophages through the scavenger receptor pathway. Bovine albumin modified by oxidation products also showed greatly accelerated degradation by macrophages. When analyzed by reverse-phase high pressure liquid chromatogrpahy, the reactive oxidation products appeared less polar than **fatty acids** or simple

medium-chain aldehydes. When treated with the carbonyl reagent 2,4-dinitrophenylhydr[redacted]ne, the reactive fractions yie[redacted]d derivatives, some of which were identified by mass spectrometry as hydrazones of nonenal, heptenal, pentenal, and crotonaldehyde. A series of 2-unsaturated aldehydes (acrolein to 2-nonenal) were all found to modify LDL, but none of these aldehyde-modified LDLs were recognized by the scavenger receptor of macrophages and all were degraded much more slowly by these cells than LDL modified with oxidation products. Furthermore, copper-oxidized LDL had only very slight immunoreactivity toward a panel of antibodies specific for adducts of simple 2-unsaturated aldehydes. Analysis of underivatized autoxidized **fatty acids** by coupled liquid chromatography/thermospray mass spectrometry revealed compounds with m/z corresponding to M+17, M+31, and 2M+31 in fractions that were capable of modifying LDL. The unoxidized **fatty acids** showed a dominant peak at M-1. These results indicate that the scavenger receptor of macrophages can recognize different **proteins** that have been modified by lipid oxidation products. The reactive products do not appear to be simple saturated or unsaturated aldehydes, but may be more complex oxygen-containing compounds. Recognition of oxidized LDL by the scavenger receptor can be accounted for by the derivatization of apolipoprotein B by such **fatty** acyl oxidation products.

1989
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Set	Items	Description
S1	630	ADIPOCYT? AND FATTY AND ACID AND BINDING AND PROTEIN?
S2	1547	AFABP OR AP2
S3	2049	S1 OR S2
S4	590	S3 AND (INHIBIT? OR TREAT?)
S5	0	S4 AND ATHEROSCLEROSIS
S6	8	S1 AND ATHEROSCLERO?
S7	5	RD (unique items)
S8	9	S2 AND ATHEROSCLERO?
S9	6	RD (unique items)
S10	0	S4 AND ARTER?
S11	35824	ATHEROSCLEROSIS AND ARTER?
S12	0	S11 AND AFABP
S13	27	S11 AND FATTY? AND ACID? AND BIND? AND PROTEIN?
S14	24	RD (unique items)

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14/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11598710 21373907 PMID: 11481226
Absence of adipocyte **fatty acid binding protein** prevents the development of accelerated **atherosclerosis** in hypercholesterolemic mice.
Perrella MA; Pellacani A; Layne MD; Patel A; Zhao D; Schreiber BM; Storch J; Feinberg MW; Hsieh CM; Haber E; Lee ME
Program of Developmental Cardiovascular Biology, Cardiovascular Division, and. Pulmonary and Critical Care Division, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA. mperrella@rics.bwh.harvard.edu
FASEB journal (United States) Aug 2001, 15 (10) p1774-6, ISSN 0892-6638 Journal Code: FAS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

14/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11443532 21279103 PMID: 11385507
Lack of macrophage **fatty-acid-binding protein** aP2 protects mice deficient in apolipoprotein E against **atherosclerosis**.
Makowski L; Boord JB; Maeda K; Babaev VR; Uysal KT; Morgan MA; Parker RA; Suttles J; Fazio S; Hotamisligil GS; Linton MF
Division of Biological Sciences and Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, USA.
Nature medicine (United States) Jun 2001, 7 (6) p699-705, ISSN 1078-8956 Journal Code: CG5
Contract/Grant No.: HL65405-01, HL, NHLBI; T32 DK7061, DK, NIDDK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The adipocyte **fatty-acid-binding protein**, aP2, has an important role in regulating systemic insulin resistance and lipid metabolism. Here we demonstrate that aP2 is also expressed in macrophages, has a significant role in their biological responses and contributes to the development of **atherosclerosis** . Apolipoprotein E (ApoE)-deficient mice also deficient for aP2 showed protection from **atherosclerosis** in the absence of significant differences in serum lipids or insulin sensitivity. aP2-deficient macrophages showed alterations in inflammatory cytokine production and a reduced ability to accumulate cholesterol esters when exposed to modified lipoproteins. Apoe-/- mice with Ap2+/+ adipocytes and Ap2-/- macrophages generated by bone-marrow transplantation showed a comparable reduction in atherosclerotic lesions to those with total aP2 deficiency, indicating an independent role for macrophage aP2 in atherogenesis. Through its distinct actions in adipocytes and macrophages, aP2 provides a link between features of the metabolic syndrome and could be a new therapeutic target for the prevention of **atherosclerosis**.

14/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11339515 21255090 PMID: 11356390
Plasma vascular endothelial growth factor and its receptor Flt-1 in patients with hyperlipidemia and **atherosclerosis** and the effects of fluvastatin or fenofibrate.
Blann AD; Belgore FM; Constans J; Conri C; Lip GY
Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, United Kingdom. a.blann@bham.ac.uk
American journal of cardiology (United States) May 15 2001, 87 (10) p1160-3, ISSN 0002-9149 Journal Code: 3DQ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Increased vascular endothelial cell growth factor (VEGF) may be important in cardiovascular pathophysiology (perhaps relating to angiogenesis and collateral vessel development) and **binds** target endothelium via receptors such as Flt-1. We hypothesized that there would be increased levels of plasma VEGF and Flt-1 in patients with **atherosclerosis** and others with hyperlipidemia compared with controls, and a reduction in these factors with 3 months of lipid-lowering therapy. Twenty patients with uncomplicated hyperlipidemia but no **atherosclerosis**, 20 patients with hyperlipidemia plus clear **atherosclerosis**, and 40 matched controls were studied. Plasma VEGF was higher in patient groups than in healthy controls ($p < 0.01$), but Flt-1 was not significantly altered. After lipid-lowering therapy, patients with uncomplicated hyperlipidemia had significantly reduced total cholesterol and VEGF (all $p < 0.05$) but no significant change in Flt-1. Lack of a significant correlation between the von Willebrand factor and VEGF suggests the latter is unrelated to endothelial damage. Plasma VEGF that increases in patients with

uncomplicated hyperlipidemia free of major underlying **atherosclerosis** and in patients with h[redacted]lipidemia plus established **at[redacted]osclerosis** is reduced by successful lipid-lowering treatment. These findings may have implications for the pathophysiology and treatment of hyperlipidemia and **atherosclerosis** , and suggest an alternative mechanism (i.e., modulation of angiogenesis) by which lipid-lowering therapy may reduce cardiovascular events beyond lipid reduction alone.

14/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11076766 21155097 PMID: 11229885
Postprandial lipoproteins and **atherosclerosis**.
Yu KC; Cooper AD
Research Institute, Ames Building, Palo Alto Medical Foundation 795 El Camino Real, Palo Alto, CA 94301.
Frontiers in bioscience (United States) Mar 1 2001, 6 pD332-54, ISSN 1093-4715 Journal Code: CUE
Languages: ENGLISH
Document type: Journal Article
Record type: In Process
During the postprandial state, dietary lipid is transported from the intestine to peripheral tissues by plasma lipoproteins called chylomicrons. In the capillary beds of peripheral tissues, chylomicron triglycerides are lipolyzed by the enzyme, lipoprotein lipase, allowing the delivery of free **fatty acids** to the cells. As a result, this produces a new particle of smaller size and enriched with cholesteryl ester referred to as chylomicron remnants. These particles are rapidly removed from the blood primarily by the liver. The liver has a complex chylomicron remnant removal system which is comprised of a combination of different mechanisms that include the low-density-lipoprotein receptor (LDLR) and the LDLR-related-**protein** (LRP). Furthermore, it has been suggested that there is a sequestration component whereby chylomicron remnants **bind** to heparan sulfate proteoglycans (HSPG) and/or hepatic lipase; this is then followed by transport to one or both of the above receptors for hepatic uptake. Over the years, a major concern has arisen about the association of chylomicron remnants and coronary heart disease (CHD) in man. Slow removal of chylomicron remnants, as reflected by a prolonged postprandial state, is now commonly observed in patients with CHD and those that have abnormal lipid disorders such as hypertriglyceridemia, familial hypercholesterolemia, familial combined hyperlipidemia and non-insulin-dependent-diabetes-mellitus. The present review will focus on (a) the details of the metabolic pathway (exogenous pathway) that describes the two-step processing of postprandial lipoproteins, (b) the role of the liver, the receptors, and the importance of efficient removal of chylomicron remnants from the blood circulation, and (c) the potential atherogenic effects of chylomicron remnants on the **arterial** wall.

14/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10905315 20568530 PMID: 11116101
Fluvastatin upregulates inducible nitric oxide synthase expression in cytokine-stimulated vascular smooth muscle cells.
Chen H; Ikeda U; Shimpo M; Ikeda M; Minota S; Shimada K
Department of Cardiology, Jichi Medical School, and the Health Science Center, Utsunomiya University, Tochigi, Japan.
Hypertension (UNITED STATES) Dec 2000, 36 (6) p923-8, ISSN 1524-4563 Journal Code: DCZ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Nitric oxide (NO) production by inducible NO synthase (iNOS) may play an

important role in the pathogenesis of **atherosclerosis**. Although fluvastatin has been shown to reduce progression of **atherosclerosis**, it is not known whether it regulates iNOS expression. We investigated the effects of fluvastatin on iNOS expression and subsequent NO synthesis in vascular smooth muscle cells (VSMCs) and the mechanism by which fluvastatin exerts its effects. Fluvastatin significantly increased interleukin-1ss (IL-1ss)-induced nitrite production by VSMCs in a time-dependent (0 to 24 hours) and dose-dependent (10(-)(8) to 10(-)(5) mol/L) manner. Increased nitrite production by fluvastatin was accompanied by increased iNOS mRNA and **protein** accumulation. IL-1ss induced nuclear factor-kappaB activation in VSMCs, which was not affected by fluvastatin. Exogenous mevalonate significantly prevented the stimulatory effect of fluvastatin on nitrite production. Cotreatment with geranylgeranyl-pyrophosphate also reversed the effect of fluvastatin. Furthermore, both Rho inhibitor C3 exoenzyme and Rho kinase inhibitor Y-27632 significantly increased IL-1ss-induced nitrite accumulation in VSMCs. These results demonstrated that fluvastatin upregulates iNOS expression and subsequent NO formation in rat VSMCs through inhibition of Rho.

14/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10868966 20455349 PMID: 10998459
Intestinal **fatty acid binding protein** polymorphism at codon 54 is not associated with postprandial responses to fat and glucose tolerance tests in healthy young Europeans. Results from EARS II participants.

Tahvanainen E; Molin M; Vainio S; Tiret L; Nicaud V; Farinaro E; Masana L ; Ehnholm C
Department of Biochemistry, National Public Health Institute, Mannerheimintie 166, 00300, Helsinki, Finland. esa tahvanainen@merck.com

Atherosclerosis (IRELAND) Oct 2000, 152 (2) p317-25, ISSN 0021-9150 Journal Code: 95X
Languages: ENGLISH
Document type: Journal Article; Multicenter Study
Record type: Completed

Polymorphism Ala54Thr of the intestinal **fatty acid-binding protein** 2 (FABP2) has been reported to have an effect on the **protein**'s affinity for long chain **fatty acids** and to be associated with serum lipid and insulin levels in fasting and especially postprandial states. We wanted to test whether this genetic variation is associated with fasting and postprandial glucose, insulin or lipid levels in 666 male university students participating in the second European **Atherosclerosis** Study (EARS II). We also studied whether the subgroup of 330 students with paternal history of myocardial infarction (MI) before the age of 55 have different genotype distribution than 336 matched controls. RESULTS: No difference in genotype distribution was observed between offspring with and without paternal history of MI or between populations from 11 European countries. The frequency of the threonine encoding allele was 0.276 in cases and 0.266 in controls. There were no differences in fasting or postprandial serum lipid, glucose or insulin levels between subjects having different genotypes. CONCLUSIONS: In this study FABP2 Ala54Thr polymorphism was not associated with lipid or glucose metabolism. In addition to environmental and genetic factors, selection of study population also may explain the difference between this and earlier studies.

14/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10820902 20464916 PMID: 11007963
Role of the peroxisome proliferator-activated receptors (PPAR) in **atherosclerosis**.

Neve BP; Fruchart JC; Staels B
Departement d'Atherosclerose, U.325 INSERM, Institut Pasteur de Lille, France.
Biochemical pharmacology (ENGLAND) Oct 15 2000, 60 (8) p1245-50, ISSN 0006-2952 Journal Code: 9Z4
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed

Peroxisome proliferator-activated receptors (PPAR) are ligand-activated transcription factors which form a subfamily of the nuclear receptor gene family. PPAR activators have effects on both metabolic risk factors and on vascular inflammation related to **atherosclerosis**. PPAR have profound effects on the metabolism of lipoproteins and **fatty acids**. PPAR alpha **binds** hypolipidemic fibrates, whereas PPAR gamma has a high affinity for antidiabetic glitazones. Both PPAR are activated by **fatty acids** and their derivatives. Activation of PPAR alpha increases the catabolism of **fatty acids** at several levels. In the liver, it increases uptake of **fatty acids** and activates their beta-oxidation. The effects that PPAR alpha exerts on triglyceride-rich lipoproteins is due to their stimulation of lipoprotein lipase and repression of apolipoprotein CIII expression, while the effects on high-density lipoproteins depend upon the regulation of apolipoproteins AI and AII. PPAR gamma has profound effects on the differentiation and function of adipose tissue, where it is highly expressed. PPAR are also expressed in atherosclerotic lesions. PPAR are present in vascular endothelial cells, smooth muscle cells, monocytes, and monocyte-derived macrophages. Via negative regulation of nuclear factor-kappa B and activator **protein** -1 signalling pathways, PPAR alpha inhibits expression of inflammatory genes, such as interleukin-6, cyclooxygenase-2, and endothelin-1. Furthermore, PPAR alpha inhibits expression of monocyte-recruiting **proteins** such as vascular cell adhesion molecule (VCAM)-1 and induces apoptosis in monocyte-derived macrophages. PPAR gamma activation in macrophages and foam cells inhibits the expression of activated genes such as inducible nitric oxide synthase, matrix metalloproteinase-9 and scavenger receptor A. PPAR gamma may also affect the recruitment of monocytes in atherosclerotic lesions as it is involved in the expression of VCAM-1 and intracellular adhesion molecule-1 in vascular endothelial cells. The involvement of PPAR in **atherosclerosis** , a disease with a chronic inflammatory character, suggests that they may play a role in other inflammatory-related diseases as well.

14/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10808446 99408498 PMID: 10480621

Variants of the insulin receptor substrate-1 and **fatty acid binding protein** 2 genes and the risk of type 2 diabetes, obesity, and hyperinsulinemia in African-Americans: the **Atherosclerosis** Risk in Communities Study.
Lei HH; Coresh J; Shuldiner AR; Boerwinkle E; Brancati FL
Department of Epidemiology, the Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland, USA.
Diabetes (UNITED STATES) Sep 1999, 48 (9) p1868-72, ISSN 0012-1797 Journal Code: E8X
Contract/Grant No.: N01-HC-55015, HC, NHLBI; N01-HC-55016, HC, NHLBI; N01-HC-55018, HC, NHLBI; +
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

We conducted a community-based case-control study of African-American men and women in the **Atherosclerosis** Risk in Communities Study. The allele frequencies of the Gly972Arg variant of the insulin receptor substrate-1 (IRS-1) gene and the Ala54Thr variant of the **fatty**

acid binding protein 2 (FABP2) gene were compared in 992 normal control subjects and three patient groups: 1) [redacted] type 2 diabetic individuals, 2) 260 severely obese individuals, and 3) 258 markedly hyperinsulinemic individuals without diabetes. Allele frequencies of Gly972Arg IRS-1 and Ala54Thr FABP2 were 0.07 and 0.22, respectively; there were no differences in allele or genotype frequencies between patients and control subjects for either gene variant. In weighted linear regression of all patients and control subjects, the presence of the IRS-1 gene variant was associated with a 0.85 (0.42) kg/m2 higher BMI (P = 0.04). In addition, individuals with at least one IRS-1 Arg972 allele and two FABP2 Thr54 alleles had a BMI of 33.3 (7.9) kg/m2, compared with 30.0 (6.3) kg/m2 for those with neither allele (P = 0.05). These results suggest that in African-Americans, these variants in the IRS-1 and FABP2 genes are not associated with the risk of type 2 diabetes, severe obesity, or marked hyperinsulinemia, but that their independent and joint effects may be associated with small increases in BMI.

14/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10808005 99360344 PMID: 10431661

Peroxisome proliferator-activated receptor-alpha activators regulate genes governing lipoprotein metabolism, vascular inflammation and **atherosclerosis**.

Fruchart JC; Duriez P; Staels B

Department of Atherosclerosis, INSERM U325, Pasteur Institute, University of Lille II, France. Jean-Charles.Fruchart@pasteur-lille.fr

Current opinion in lipidology (ENGLAND) Jun 1999, 10 (3) p245-57, ISSN 0957-9672 Journal Code: B05

Languages: ENGLISH

Document type: Journal Article; Review; Review, Tutorial

Record type: Completed

The peroxisome proliferator-activated receptors (PPARs) [alpha, delta (beta) and gamma] form a subfamily of the nuclear receptor gene family. All PPARs are, albeit to different extents, activated by **fatty acids** and derivatives; PPAR-alpha **binds** the hypolipidemic fibrates whereas antidiabetic glitazones are ligands for PPAR-gamma. PPAR-alpha activation mediates pleiotropic effects such as stimulation of lipid oxidation, alteration in lipoprotein metabolism and inhibition of vascular inflammation. PPAR-alpha activators increase hepatic uptake and the esterification of free **fatty acids** by stimulating the **fatty acid** transport **protein** and acyl-CoA synthetase expression. In skeletal muscle and heart, PPAR-alpha increases mitochondrial free **fatty acid** uptake and the resulting free **fatty acid** oxidation through stimulating the muscle-type carnitine palmitoyltransferase-I. The effect of fibrates on the metabolism of triglyceride-rich lipoproteins is due to a PPAR-alpha dependent stimulation of lipoprotein lipase and an inhibition of apolipoprotein C-III expressions, whereas the increase in plasma HDL cholesterol depends on an overexpression of apolipoprotein A-I and apolipoprotein A-II. PPARs are also expressed in atherosclerotic lesions. PPAR-alpha is present in endothelial and smooth muscle cells, monocytes and monocyte-derived macrophages. It inhibits inducible nitric oxide synthase in macrophages and prevents the IL-1-induced expression of IL-6 and cyclooxygenase-2, as well as thrombin-induced endothelin-1 expression, as a result of a negative transcriptional regulation of the nuclear factor-kappa B and activator **protein**-1 signalling pathways. PPAR activation also induces apoptosis in human monocyte-derived macrophages most likely through inhibition of nuclear factor-kappa B activity. Therefore, the pleiotropic effects of PPAR-alpha activators on the plasma lipid profile and vascular wall inflammation certainly participate in the inhibition of **atherosclerosis** development observed in angiographically documented intervention trials with fibrates.

14/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10803571 99257364 PMID: 10323782
Role of group II secretory phospholipase A2 in **atherosclerosis**: 2. Potential involvement of biologically active oxidized phospholipids.
Leitinger N; Watson AD; Hama SY; Ivandic B; Qiao JH; Huber J; Faull KF; Grass DS; Navab M; Fogelman AM; de Beer FC; Lusis AJ; Berliner JA
Department of Medicine, University of California, Los Angeles, USA.
Arteriosclerosis, thrombosis, and vascular biology (UNITED STATES) May 1999, 19 (5) p1291-8, ISSN 1079-5642 Journal Code: B89
Contract/Grant No.: AG10886, AG, NIA; HL30568, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Secretory nonpancreatic phospholipase A2 (group II sPLA2) is induced in inflammation and present in atherosclerotic lesions. In an accompanying publication we demonstrate that transgenic mice expressing group II sPLA2 developed severe **atherosclerosis**. The current study was undertaken to determine whether 1 mechanism by which group II sPLA2 might contribute to the progression of inflammation and **atherosclerosis** is by increasing the formation of biologically active oxidized phospholipids. In vivo measurements of bioactive lipids were performed, and in vitro studies tested the hypothesis that sPLA2 can increase the accumulation of bioactive phospholipids. We have shown previously that 3 oxidized phospholipids derived from the oxidation of 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (PAPC) stimulated endothelial cells to **bind** monocytes, a process that is known to be an important step in atherogenesis. We now show that these 3 biologically active phospholipids are significantly increased in livers of sPLA2 transgenic mice fed a high-fat diet as compared with nontransgenic littermates. We present in vitro evidence for several mechanisms by which these phospholipids may be increased in sPLA2 transgenics. These studies demonstrated that polyunsaturated free **fatty acids** , which are liberated by sPLA2, increased the formation of bioactive phospholipids in LDL, resulting in increased ability to stimulate monocyte-endothelial interactions. Moreover, sPLA2-treated LDL was oxidized by cocultures of human aortic endothelial cells and smooth muscle cells more efficiently than untreated LDL. Analysis by electrospray ionization-mass spectrometry revealed that the bioactive phospholipids, compared with unoxidized PAPC, were less susceptible to hydrolysis by human recombinant group II sPLA2. In addition, HDL from the transgenic mice and human HDL treated with recombinant sPLA2 in vitro failed, in the coculture system, to protect against the formation of biologically active phospholipids in LDL. This lack of protection may in part relate to the decreased levels of paraoxonase seen in the HDL isolated from the transgenic animals. Taken together, these studies show that levels of biologically active oxidized phospholipids are increased in sPLA2 transgenic mice; they also suggest that this increase may be mediated by effects of sPLA2 on both LDL and HDL.

14/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10774057 20144293 PMID: 10680041
Regulation of macrophage gene expression by peroxisome-proliferator-activated receptor gamma: implications for cardiovascular disease.
Tontonoz P; Nagy L
Department of Pathology, University of California, Los Angeles 90095, USA. ptontonoz@mednet.ucla.edu
Current opinion in lipidology (ENGLAND) Dec 1999, 10 (6) p485-90, ISSN 0957-9672 Journal Code: B05
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial

Record type: Complete

The peroxisome-proliferator-activated receptor gamma a member of the nuclear receptor superfamily that functions as a key transcriptional regulator of cell differentiation and lipid metabolism. In addition, peroxisome-proliferator-activated receptor gamma is now recognized to be the biological receptor for the thiazolidinedione class of antidiabetic drugs, which includes troglitazone and rosiglitazone. Recent evidence indicates that peroxisome-proliferator-activated receptor gamma is expressed at high levels in macrophages, including the foam cells of atherosclerotic lesions. Oxidized low-density lipoprotein, which plays a central role in lesion development, can activate peroxisome-proliferator-activated receptor gamma by providing the cell with oxidized **fatty acid** ligands of the receptor. The elucidation of a peroxisome-proliferator-activated receptor gamma signalling pathway in macrophages provides a mechanism by which oxidized lipids may directly regulate gene expression in the context of the atherosclerotic lesions. A number of potential target genes for peroxisome-proliferator-activated receptor gamma in these cells have been identified. Some, such as the type B scavenger receptor CD36 are induced by peroxisome-proliferator-activated receptor gamma ligands, whereas others, such as scavenger receptor type A, inducible nitric oxide synthetase and certain cytokines, are repressed. Given the widespread clinical use of thiazolidinediones, it is important to consider the influence of these drugs on the risk of **atherosclerosis**. The net effect of peroxisome-proliferator-activated receptor gamma ligands on the atherogenic process is likely to reflect a balance between local effects in the **artery** wall and systemic effects on lipid metabolism.

14/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10748308 98226736 PMID: 9560197

Protein-bound acrolein: potential markers for oxidative stress.

Uchida K; Kanematsu M; Sakai K; Matsuda T; Hattori N; Mizuno Y; Suzuki D; Miyata T; Noguchi N; Niki E; Osawa T

Laboratory of Food and Biodynamics, Nagoya University Graduate School of Bioagricultural Sciences, Nagoya 464-8601, Japan. uchidak@agr.nagoya-u.ac.jp

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Apr 28 1998, 95 (9) p4882-7, ISSN 0027-8424
Journal Code: PV3

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Acrolein (CH2==CH---CHO) is known as a ubiquitous pollutant in the environment. Here we show that this notorious aldehyde is not just a pollutant, but also a lipid peroxidation product that could be ubiquitously generated in biological systems. Upon incubation with BSA, acrolein was rapidly incorporated into the **protein** and generated the **protein**-linked carbonyl derivative, a putative marker of oxidatively modified **proteins** under oxidative stress. To verify the presence of **protein**-bound acrolein in vivo, the mAb (mAb5F6) against the acrolein-modified keyhole limpet hemocyanin was raised. It was found that the acrolein-lysine adduct, Nepsilon-(3-formyl-3, 4-dehydropiperidino)lysine, constitutes an epitope of the antibody. Immunohistochemical analysis of atherosclerotic lesions from a human aorta demonstrated that antigenic materials recognized by mAb5F6 indeed constituted the lesions, in which intense positivity was associated primarily with macrophage-derived foam cells and the thickening neointima of **arterial** walls. The observations that (i) oxidative modification of low-density lipoprotein with Cu2+ generated the acrolein-low-density lipoprotein adducts and (ii) the iron-catalyzed oxidation of arachidonate in the presence of **protein** resulted in the formation of antigenic materials suggested that polyunsaturated **fatty acids** are sources of acrolein that cause the production of **protein**-bound acrolein. These data suggest

that the **protein** -bou[redacted] acrolein represents potential markers of oxidative stress and long-term damage to **protei**[redacted]n aging, **atherosclerosis**, and diabetes.

14/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10743800 98102597 PMID: 9439479
Metabolism of native and naturally occurring multiple modified low density lipoprotein in smooth muscle cells of human aortic intima.
Tertov VV; Orekhov AN
Institute of Experimental Cardiology, Cardiology Research Center, Moscow, Russia.
Experimental and molecular pathology (UNITED STATES) 1997, 64 (3) p127-45, ISSN 0014-4800 Journal Code: EQ5
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The subfraction of low density lipoprotein (LDL) with low sialic **acid** content that caused accumulation of cholesterol esters in human aortic smooth muscle cells has been found in the blood of coronary **atherosclerosis** patients. It was demonstrated that this subfraction consists of LDL with small size, high electronegative charge, reduced lipid content, altered tertiary structure of apolipoprotein B, etc. LDL of this subfraction is naturally occurring multiple-modified LDL (nomLDL). In this study we compared the **binding**, uptake and proteolytic degradation of native LDL and nomLDL by smooth muscle cells cultured from human grossly normal intima, **fatty** streaks, and atherosclerotic plaques. Uptake of nomLDL by normal and atherosclerotic cells was 3.5- and 6-fold, respectively, higher than uptake of native LDL. Increased uptake of nomLDL was due to increased **binding** of this LDL by intimal smooth muscle cells. The enhanced **binding** is explained by the interaction of nomLDL with cellular receptors other than LDL-receptor. Modified LDL interacted with the scavenger receptor, asialoglycoprotein receptor, and also with cell surface proteoglycans. Rates of degradation of nomLDL were 1.5- and 5-fold lower than degradation of native LDL by normal and atherosclerotic cells, respectively. A low rate of nomLDL degradation was also demonstrated in homogenates of intimal cells. Activities of lysosomal **proteinases** of atherosclerotic cells were decreased compared with normal cells. Pepstatin A, a cathepsin D inhibitor, completely inhibited lipoprotein degradation, while serine, thiol, or metallo-**proteinase** inhibitors had partial effect. This fact reveals that cathepsin D is involved in initial stages of apoB degradation by intimal smooth muscle cells. Obtained data show that increased uptake and decreased lysosomal degradation of nomLDL may be the main cause of LDL accumulation in human aortic smooth muscle cells, leading to foam cell formation.

14/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10452302 20084754 PMID: 10617950
Zinc protects against apoptosis of endothelial cells induced by linoleic **acid** and tumor necrosis factor alpha.
Meerarani P; Ramadass P; Toborek M; Bauer HC; Bauer H; Hennig B
Departments of Nutrition and Food Science and Surgery, University of Kentucky, Lexington, and the Molecular Biology Institute, Austrian Academy of Sciences, Salzburg.
American journal of clinical nutrition (UNITED STATES) Jan 2000, 71 (1) p81-7, ISSN 0002-9165 Journal Code: 3EY
Contract/Grant No.: 1 P42 ES 07380, ES, NIEHS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

BACKGROUND: Zinc requirements of the vascular endothelium may be increased in inflammatory conditions, ie, **atherosclerosis**, in which apoptotic cell death is prevalent. OBJECTIVE: We hypothesized that zinc deficiency may potentiate disruption of endothelial cell integrity mediated by **fatty acids** and inflammatory cytokines by enhancing pathways that lead to apoptosis and up-regulation of caspase genes. DESIGN: Endothelial cells were maintained in low-serum medium or grown in culture media containing selected chelators, ie, diethylenetriaminepentaacetate or N,N,N', N'-tetrakis(2-pyridylmethyl)-ethylenediamine (TPEN), with or without zinc supplementation. Subsequently, cells were treated with linoleic **acid**, tumor necrosis factor alpha (TNF-alpha), or both. We studied the effect of zinc deficiency and supplementation on the induction of apoptosis by measuring caspase-3 activity, cell **binding** of annexin V, and DNA fragmentation. RESULTS: Our results indicated that linoleic **acid** and TNF-alpha independently, but more markedly in concert, up-regulated caspase-3 activity and induced annexin V **binding** and DNA fragmentation. Zinc deficiency, especially when induced by TPEN, dramatically increased apoptotic cell death induced by cytokines and lipids compared with control cultures. Supplementation of low-serum- or chelator-treated endothelial cells with physiologic amounts of zinc caused a marked attenuation of apoptosis induced by linoleic **acid** and TNF-alpha. Morphologic changes of cells observed during zinc deficiency were prevented by zinc supplementation. Media supplementation with other divalent cations (eg, calcium and magnesium) did not mimic the protective role of zinc against apoptosis. CONCLUSIONS: Our data indicate that zinc is vital to vascular endothelial cell integrity, possibly by regulating signaling events to inhibit apoptotic cell death.

14/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09529368 97312342 PMID: 9168783

Induction of P-selectin by oxidized lipoproteins. Separate effects on synthesis and surface expression.

Vora DK; Fang ZT; Liva SM; Tyner TR; Parhami F; Watson AD; Drake TA; Territo MC; Berliner JA

Department of Medicine, University of California, Los Angeles 90024, USA.

Circulation research (UNITED STATES) Jun 1997, 80 (6) p810-8, ISSN 0009-7330 Journal Code: DAJ

Contract/Grant No.: HL-07412, HL, NHLBI; HL-30568, HL, NHLBI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

Leukocyte **binding** to the endothelium is one of the earliest events in the occurrence of **atherosclerosis**. Leukocyte adhesion molecules involved in this process have not been definitely identified. We have found that treatment of human aortic endothelial cells (HAECs) with minimally modified low-density lipoprotein (MM-LDL) for 24 hours caused a 2- to 3-fold increase of P-selectin **protein**, with little change in P-selectin surface expression. A 15-minute histamine treatment of cells exposed to MM-LDL caused a 50% to 100% increase in P-selectin surface expression compared with cells not treated with the lipoprotein. This increase resulted in a 2-fold increase in **binding** of leukocytes to the endothelium. Immunostaining of permeabilized HAECs after MM-LDL treatment also revealed a highly reproducible increase in intracellular P-selectin associated with rod-shaped structures, typical of Weibel-Palade bodies. Oxidized phospholipids were shown to be mainly responsible for the action of MM-LDL. This increased P-selectin expression was associated with MM-LDL-induced cAMP elevation. Like histamine, highly oxidized low-density lipoprotein, especially the oxidized **fatty acids**, caused immediate redistribution of P-selectin to the cell surface followed by reinternalization. Immunohistochemical staining showed that endothelial cells on human **fatty** streak lesions expressed increased levels of P-selectin compared with nonlesion areas. These studies suggest that

P-selectin may play an important role in early recruitment of mononuclear cells to the subendothelium in human **atherosclerosis** and that oxidized lipoproteins may contribute to the increased expression of this molecule by increasing intracellular stores and causing redistribution to the cell surface.

14/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09520232 97017635 PMID: 8864252
Relation of C4b-**binding protein** to athero-sclerosis of the descending thoracic aorta.
Kimoto K; Inoue T; Oku K; Mori T; Kusuda M; Handa K; Sakata N; Sasaki J; Arakawa K
Department of Internal Medicine, School of Medicine, Fukuoka University, Japan.
Artery (UNITED STATES) 1996, 22 (2) p101-14, ISSN 0098-6127 Journal Code: 8NN
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
C4b **binding protein** (C4bp) is a regulator of the classical pathway of the complementing system. It forms a complex with **protein** S which serves as a cofactor of coagulation inhibitor, **protein** C. We have reported that C4bp is an acute phase reactant and associated with total cholesterol and triglyceride concentrations (Biochim. Biophys. Acta 963 (1988) 98-108). This suggests a possible association of C4bp with athero-sclerosis. We examined the relation of C4bp levels and the severity of **atherosclerosis** of the descending thoracic aorta in 98 Japanese men. The severity of aortic **atherosclerosis** was assessed by average sclerotic length (ASL) and average sclerotic area (ASA), using transesophageal echocardiography. After adjustment for age, C4bp levels increased significantly with increasing ASL and ASA. The association remained significant even after adjusting for total cholesterol, hypertension, smoking, drinking, body mass index, fasting blood sugar, and uric **acid** . Immunohistochemical analysis of specimens of the descending thoracic aorta from autopsies, demonstrated the presence of C4bp in the foamy macrophages of **fatty** streaks and the necrotic core of atheromatous plaque. These findings indicate that the serum level of C4bp can serve as an independent indicator of aortic athero-sclerosis.

14/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08740495 95408292 PMID: 7677772
Apolipoprotein B-bound lipids as a marker for evaluation of low density lipoprotein oxidation in vivo.
Tertov VV; Kaplun VV; Dvoryantsev SN; Orekhov AN
Institute of Experimental Cardiology, Russian Academy of Science, Moscow.
Biochemical and biophysical research communications (UNITED STATES) Sep 14 1995, 214 (2) p608-13, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
It has been generally accepted that oxidized low density lipoprotein (LDL) plays an important role in atherogenesis. However, oxidized LDL was not detected in patients' blood and the extent of LDL oxidation in vivo is unknown. We have suggested that LDL oxidation may lead to a formation of covalent links between lipids and apolipoprotein B. LDL were oxidized by copper ions, 2,2'-azobis-(2-aminopropane hydrochloride), sodium hypochlorite or by incubation with macrophages. Oxidized LDL were delipidated by repeated extraction with organic solvents. After mild alkaline hydrolysis **protein** -bound sterols were identified

colorimetrically and by high-performance liquid chromatography. **Protein**-bound phospholipid residues were detected by nuclear magnetic resonance and colorimetric determination of phosphate. Using radiolabeled lipids it was also shown that free and esterified cholesterol, phospholipids, as well as triglyceride and free **fatty acid** residues can form covalent bonds with apolipoprotein B. The ability of lipids to **bind** to apolipoprotein B correlates with the degree of unsaturation of their **fatty acids** and depends on the nature of polar head of phospholipids. When LDL were oxidized with copper ions, the content of **protein** -bound lipids increased gradually up to 24 h of incubation, while the levels of conjugated dienes, hydroperoxides and thiobarbituric **acid** -reactive substances changed in varying manners. It has been demonstrated that the content of **protein**-bound sterols in multiple-modified desialylated LDL of patients with coronary **atherosclerosis** is higher than that in native LDL. Our results suggest that the level of **protein**-bound lipids may be a marker of LDL oxidation and can be used to evaluate the association of lipoprotein oxidation and atherogenesis.

14/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08067885 91070963 PMID: 2253471
Arterial fatty acid-binding protein activity associated with dietarily-induced and spontaneously occurring **atherosclerosis** in the rabbit (Oryctolagus cuniculus).
St John LC; Bell FP
Metabolic Diseases Research, Upjohn Company, Kalamazoo, MI 49001.
Comparative biochemistry and physiology (ENGLAND) 1990, 97 (1) p123-7, ISSN 0305-0491 Journal Code: DNV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. Adult WHHL rabbits, or New Zealand rabbits fed either a stock chow diet or a high cholesterol diet were evaluated to assess the relationship between the development of aortic **atherosclerosis** and **arterial** FABP activity. 2. Aortic FABP activity was significantly (P less than 0.05) lower in atherosclerotic New Zealand aortas (0.039 +/- 0.008 nmol palmitoyl CoA bound/mg soluble prot) which had developed macroscopic lesions on 80% of the aortic surface as compared to lesion-free New Zealand aortas (0.053 +/- 0.002 nmol palmitoyl CoA bound/mg soluble prot). 3. In spontaneously hyperlipidemic rabbit (WHHL) aortas, FABP activity (0.023 +/- 0.004 nmol palmitoyl CoA bound/mg soluble prot) was significantly lower (P less than 0.05) than in either the normal or atherosclerotic New Zealand aortas. 4. To our knowledge, this study is the first to report a change in **arterial** FABP with the atherogenic process.

14/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07184857 92370947 PMID: 1354584
Temporal evaluation of **fatty acid-binding protein** (FABP) activity in association with the development of **atherosclerosis** in the rabbit.
St John LC; Bell FP
Upjohn Laboratories, Upjohn Company, Kalamazoo, MI 49001.
Comparative biochemistry and physiology (ENGLAND) Jun 1992, 102 (2) p357-61, Journal Code: B59
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
1. The relationship between **atherosclerosis** development and changes in **arterial fatty acid binding protein** (FABP)

activity was investigated in the aortas of New Zealand rabbits which were fed an atherogenic diet containing 1% cholesterol and 3% peanut oil for 16 weeks. 2. At 4-week intervals, FABP activity, cholesterol and microsomal acylCoA:cholesterol acyltransferase (ACAT) activity were determined in aortic tissue and serum cholesterol was measured; age-matched normal rabbits served as control comparators. 3. Serum cholesterol increased from 35 mg/dl in the normal rabbits to 2290 mg/dl in the 16-week cholesterol-fed rabbits. 4. The microsomal fraction isolated from cholesterol-fed rabbit aortas exhibited a progressive elevation in ACAT activity as time on the diet increased. By 12-16 weeks, ACAT activity had increased approximately 10-fold relative to normal activity. 5. **Arterial** cholesterol content of the cholesterol-fed animals increased from less than 2 mg/g wet weight to greater than 10 mg/g wet weight at 12 and 16 weeks. In contrast, **arterial** FABP activity gradually decreased with time on the cholesterol diet; a significant decrease (P less than 0.05) was observed at 16 weeks, where palmitoyl CoA **binding** was decreased from 61.0 to 36.3 pmol/mg **protein**. 6. In the cholesterol-fed rabbits, total **arterial** cholesterol and ACAT activity showed a significant (P less than 0.05) inverse correlation to FABP activity with correlation coefficients of -0.93 and -0.95, respectively. 7. Additionally, FABP activity increased significantly (P less than 0.05) in the 16-week normal rabbit as compared to the 4-week normal rabbit, suggesting an age-dependent interaction.

14/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07171171 92092617 PMID: 1753684

Lipid changes in the nephrotic syndrome: new insights into pathomechanisms and treatment.

D'Amico G
Divisone di Nefrologia e Dialisi, Ospedale S. Carlo Borromeo, Milano.

Klinische Wochenschrift (GERMANY) Sep 3 1991, 69 (13) p618-22,
ISSN 0023-2173 Journal Code: KWH
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed

The abnormalities of lipid metabolism in nephrotic syndrome consist in an increase in total and low-density lipoprotein (LDL) cholesterol, apolipoproteins B (ApoB), C-II and C-III, associated in patients with heavier or marked hypoalbuminemia with an increase in triglycerides and very low-density lipoprotein (VLDL) cholesterol, while the high-density lipoproteins (HDL) are distributed abnormally (increased HDL3 fraction and decreased HDL2 fraction) and the Apo A-I to Apo B ratio is reduced. Both increased hepatic lipoprotein synthesis and reduced removal capacity contribute to this hyperlipidemia. **Proteinuria** may lead to the lipoprotein abnormalities through stimulation of VLDL synthesis by the liver induced by hypoalbuminemia, although it has been more recently suggested that urinary **protein** loss is associated with the urinary loss of some important cofactor for the regulation of lipid synthesis or catabolism. Treatment of lipid abnormalities in patients with long-lasting heavy **proteinuria** is mandatory, because they may cause or contribute to accelerated **atherosclerosis** , but also because they appear to accelerate progression of renal disease by favouring mesangial sclerosis. Four groups of lipid-lowering drugs have been tested: 1) bile **acid-binding** resins; 2) fibric **acid**; 3) probucol; 4) inhibitors of HMG CoA reductase. The drugs of the last group appear to be effective and safe in short-term experiments, but long-term studies are necessary to confirm their validity. A dietary approach, consisting in a strictly vegetarian soy diet, very rich in poly- and monounsaturates **fatty acids** , has been recently tested by the author, with very promising results.

14/3,AB/21 (Item 1 [redacted]m file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13081183 BIOSIS NO.: 200100288332
The cholesterol quartet.
AUTHOR: Goldstein Joseph L(a); Brown Michael S(a)
AUTHOR ADDRESS: (a)Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX, 75390-9046: jgolds@mednet.swmed.edu, mbrow1@mednet.swmed.edu**USA
JOURNAL: Science (Washington D C) 292 (5520):p1310-1312 18 May, 2001
MEDIUM: print
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

14/3,AB/22 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12904474 BIOSIS NO.: 200100111623
HIV protease inhibitor-induced hyperlipidemia and lipodystrophy is mediated through regulation of sterol responsive element **binding protein** (SREBP) responsive genes.
AUTHOR: Kuhel David G(a); Woollett Laura A(a); Fichtenbaum Carl J(a); Hui David Y(a)
AUTHOR ADDRESS: (a)Univ of Cincinnati, Cincinnati, OH**USA
JOURNAL: Circulation 102 (18 Supplement):pII360 October 31, 2000
MEDIUM: print
CONFERENCE/MEETING: Abstracts from Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

14/3,AB/23 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12537860 BIOSIS NO.: 200000291362
Dietary soy-derived isoflavone phytoestrogens: Could they have a role in coronary heart disease prevention?.
AUTHOR: Tikkanen Matti J; Adlercreutz Herman
AUTHOR ADDRESS: (a)Department of Medicine, Helsinki University Central Hospital, 00290, Helsinki**Finland
JOURNAL: Biochemical Pharmacology 60 (1):p1-5 July 1, 2000
MEDIUM: print.
ISSN: 0006-2952
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Soy **protein**-containing foods are a rich source of isoflavone phytoestrogens, such as genistein and daidzein. There is great interest in these substances, as lower rates of chronic diseases, including coronary heart disease, have been associated with high dietary intake of soy-containing foods. Soy phytoestrogens **bind** weakly to

estrogen receptors, a[redacted]some **bind** more strongly to estr[redacted]gen receptor-beta compared with estrogen receptor-alpha. A[redacted]a-analysis has indicated that isoflavone phytoestrogens lowered plasma cholesterol concentrations in subjects with initially elevated levels, but had little effect in subjects with normal cholesterol concentrations. These substances reportedly may also have beneficial effects on **arterial** endothelial function. In addition to these potentially antiatherogenic effects, many laboratories are investigating other possible mechanisms, including antioxidative and antiproliferative properties of these substances. We have shown that dietary supplementation with soy-derived isoflavones reduced the in vitro oxidation susceptibility of low-density lipoprotein (LDL). To further explore this phenomenon, we incorporated genistein and daidzein into LDL molecules in vitro with the aid of an artificial transfer system. However, it was necessary to convert the isoflavone molecules to fat-soluble derivatives, **fatty acid** esters (analogous to esterified endogenous estrogens, which are known to occur in vivo), to achieve significant incorporation. The LDLs containing esterified isoflavones were shown to be less susceptible to oxidation in vitro than native LDL. We also employed U937 cell cultures for investigating the effects of isoflavone-containing LDLs on cell proliferation. Some of these LDLs exhibited antiproliferative effects in cultured U937 cells. In summary, lipophilic phytoestrogen derivatives could be incorporated into LDLs, increasing their oxidation resistance and antiproliferative efficacy ex vivo, both of which are, in theory, antiatherogenic effects. Further studies are needed to assess to what extent analogous effects could be produced in vivo and whether such substances have a role in hormone replacement and coronary heart disease prevention in postmenopausal women.

2000

14/3,AB/24 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06811629 BIOSIS NO.: 000088121073
RECOGNITION OF OXIDIZED LOW DENSITY LIPOPROTEIN BY THE SCAVENGER RECEPTOR OF MACROPHAGES RESULTS FROM DERIVATIZATION OF APOLIPOPROTEIN B BY PRODUCTS OF **FATTY ACID** PEROXIDATION
AUTHOR: STEINBRECHER U P; LOUGHEED M; KWAN W-C; DIRKS M
AUTHOR ADDRESS: DIV. GASTROENTEROL., DEP. MED., UNIV. BRITISH COLUMBIA, VANCOUVER, BRITISH COLUMBIA V6T 1W5, CANADA.
JOURNAL: J BIOL CHEM 264 (26). 1989. 15216-15223. 1989
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Uptake of cholesterol-containing lipoproteins by macrophages in the **arterial** intima is believed to be an important step in the pathogenesis of **atherosclerosis**. There are a number of possible mechanisms by which macrophages might accumulate cholesterol, and one that has attracted much interest recently involves the uptake of oxidatively modified low density lipoprotein (LDL) via a specific cell surface receptor, termed the scavenger or acetyl-LDL receptor. Previous studies have shown that chemical derivatization of LDL with reagents that result in neutralization of the charge of lysine amino groups also allows recognition by this receptor. As well, it has been shown tht oxidation of LDL is accompanied by a decrease in free lysine groups and **binding** of lipid products to apolipoprotein B. The present studies were done to further characterize the receptor-**binding** domain on oxidized LDL. It was found that LDL could be modified by incubation with water-soluble products derived from autoxidized unsaturated **fatty acids** under conditions that inhibited oxidation of the LDL itself. The LDL

modified in this way [redacted] increased electrophoretic mobility but showed no evidence of the oxidative damage that typifies LDL oxidized by exposure to metal ions. Furthermore, the oxidation product-modified LDL was rapidly degraded by cultured macrophages through the scavenger receptor pathway. Bovine albumin modified by oxidation products also showed greatly accelerated degradation by macrophages. When analyzed by reverse-phase high pressure liquid chromatogrpahy, the reactive oxidation products appeared less polar than **fatty acids** or simple medium-chain aldehydes. When treated with the carbonyl reagent 2,4-dinitrophenylhydrazine, the reactive fractions yielded derivatives, some of which were identified by mass spectrometry as hydrazones of nonenal, heptenal, pentenal, and crotonaldehyde. A series of 2-unsaturated aldehydes (acrolein to 2-nonenal) were all found to modify LDL, but none of these aldehyde-modified LDLs were recognized by the scavenger receptor of macrophages and all were degraded much more slowly by these cells than LDL modified with oxidation products. Furthermore, copper-oxidized LDL had only very slight immunoreactivity toward a panel of antibodies specific for adducts of simple 2-unsaturated aldehydes. Analysis of underivatized autoxidized **fatty acids** by coupled liquid chromatography/thermospray mass spectrometry revealed compounds with m/z corresponding to M+17, M+31, and 2M+31 in fractions that were capable of modifying LDL. The unoxidized **fatty acids** showed a dominant peak at M-1. These results indicate that the scavenger receptor of macrophages can recognize different **proteins** that have been modified by lipid oxidation products. The reactive products do not appear to be simple saturated or unsaturated aldehydes, but may be more complex oxygen-containing compounds. Recognition of oxidized LDL by the scavenger receptor can be accounted for by the derivatization of apolipoprotein B by such **fatty** acyl oxidation products.